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Safety and Efficacy of First-line Atypical Antipsychotics in Schizophrenia: Evidence Based Medicine and Clinical Practice

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Safety and Efficacy of First-line Atypical Antipsychotics in Schizophrenia: Evidence Based Medicine and Clinical Practice

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Declaration

I hereby declare that this thesis is the results of my own investigations, except where otherwise stated. All other sources are acknowledged by bibliographic references.
This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree unless, as agreed by the University, for approved dual awards.

Yr wyf drwy hyn yn datgan mai canlyniad fy ymchwil fy hun yw'r thesis hwn, ac eithrio lle nodir yn wahanol. Caiff ffynonellau eraill eu cydnabod gan droednodiadau yn rhoi cyfeiriadau eglur. Nid yw sylwedd y gwaith hwn wedi cael ei dderbyn o'r blaen ar gyfer unrhyw radd, ac nid yw'n cael ei gyflwyno ar yr un pryd mewn ymgeisiaeth am unrhyw radd oni bai ei fod, fel y cytunwyd gan y Brifysgol, am gymwysterau deuol cymeradwy.

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To my family, who shouldered the burdens and the joys of this work alongside me, tempered my exhilarations and counselled my despondencies: you were right - it was all well-worth it.

Abstract

We have a thirst for new knowledge, and medical science is quintessentially knowledge "in progress". In fact, applying 'new knowledge' is the defining ambition in practicing Evidence Based Medicine in the 21st century. However, despite the fact that new knowledge on optimal treatment options, effective interventions and patient-centred care pathways is continuously generated, its uptake in real-life clinical practice can be slow and patchy. This is particularly obvious in the treatment of patients with schizophrenia, or first episode psychosis indicative of schizophrenia, where diagnostic and therapeutic guidelines change (and are often contradictory) and research findings (often of limited methodological strength) fail to resonate with the prescribing clinician.

This body of work is the result of an investigation into the interplay of factors which determine the use (partial use/interpret/ignore) of existing evidence and Guidelines in the clinical decision-making process to prescribe / not prescribe atypical antipsychotics as first-line treatment for schizophrenia - and other factors that contribute to clinical decision-making.

I have used the change in NICE guidance as a natural experiment to examine how a change in the evidence-base translates into changes in clinical practice, and have discovered that it does not consistently do so - and decision-making seems to be on a parallel trajectory.

I am arguing that this is a false dichotomy and in fact the 'E' in EBM is a multifaceted component - and clinical decision-making *is* informed by evidence, but what constitutes evidence and how is it utilised depends on very specific individual factors and it is possible to discern distinct 'patterns'.

The implications are that guideline-makers may need to adapt, to account for different patterns of knowledge translation and utilisation, and that 'one-size fits all' approaches in producing and cascading clinical guidelines are no longer suitable.

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Preface

Chapters 2 to 4 represent the results of three interdependent studies. The design of the project as a whole, the research question and theoretical framing, the individual research project protocols and data collection, as well as the data analysis and interpretation for the scope of this thesis are my original and unique contribution.

Some of the data from each project has been used for teaching purposes and became part of postgraduate students' dissertations, under my supervision.

Some of the material in this thesis has been presented in conference abstracts, posters and/or published as journal articles, either under my sole authorship or first authorship – and these have been partially reproduced in this thesis.

Introduction to the study

This is a thesis about factors that influence the clinical-decision making process in formulating a treatment plan for patients with schizophrenia - specifically around prescribing antipsychotics. It aims to demonstrate that these factors can be identified and used to promote knowledge translation and utilisation.

Formulating a treatment plan in Mental Health is a complex issue and often more nuanced and multifaceted than a treatment plan in somatic medicine. Clinicians argue that whilst a patient is not defined by, say, their liver disease, this can be treated as extraneous to the patient. There would be life-style limitations but not as far-reaching as a mental health condition which affects the very essence of the 'being' as a somato-psycho-social whole. Furthermore, whilst in somatic medicine a treatment plan can be largely based on objective diagnostic tests and laboratory results, in psychiatry a treatment plan is often more subjective and clinicians' decision-making processes are influenced by a multitude of factors at both clinician and patient level. This study will explore these factors in the context of Evidence Based Medicine - and will demonstrate that it is possible to identify them and use them to accommodate evolving knowledge.

The study involved several steps necessary to set a robust research hypothesis and establish what type of data would most accurately support such an investigation.

The first step was to set the scene by discussing the definition of schizophrenia as a concept and available treatment options. My position was to remain impartial and present the various points of view in relation to the clinical utility of 'categorical' or 'dimensional' diagnostic frameworks and pharmacological treatment choices ('typical' or 'atypical'

antipsychotics) in an objective way, to refrain from introducing a bias in the hypothesis of the study.

The next necessary step was to explore the process of Clinical Guideline development, in particular around the prescribing recommendations in the NICE Schizophrenia guidelines, and map out changes in evidence around safety and efficacy of atypical antipsychotics that led to a change in the guideline's position on the matter.
The "NICE Clinical Guideline 1 - Schizophrenia: Core interventions in the treatment and management of schizophrenia in primary and secondary care" (National Collaborating Centre for Mental Health (Great Britain), 2003) was the first such guideline issued by the National Institute for Clinical Excellence. It was intended as a set of recommendations based on the synthesis of all existing research evidence relating to the diagnosis and management of schizophrenia to that point - and shaped clinical practice, especially prescribing practice by advocating that atypical antipsychotics should be initiated "at the earliest opportunity".

Whilst all guidelines get reviewed from time to time to ensure they stay up to date and incorporate the latest research evidence, the Clinical Guideline 1 received a radical overhaul. By re-evaluating the evidence base for prescribing in the initial guidance, a meta-analysis (Geddes, Freemantle, Harrison, & Bebbington, 2000) and Cochrane review (Hamann, Kissling, Leucht, & Rummel-Kluge, 2003) found no conclusive evidence that the atypical antipsychotic agents recommended by the initial Clinical Guideline 1 have a better efficacy, tolerability or safety profile than the established class of typical antipsychotics – and highlighted a great number of limitations in the existing studies which formed the basis for this Guideline (including a systematic methodological bias in comparator dose and called for further "pragmatic, well-designed and reported long-term trials […] to answer this question" (Hamann et al., 2003)

New research evidence from large scale publicly funded clinical trials including health economics data (Lieberman et al., 2005), (Lewis et al., 2005) found that the benefits of atypicals have been exaggerated in previously published data and in fact there was no clinical efficacy or quality of life advantage (except for clozapine).

The authors of the guideline conceded that the NICE Schizophrenia Guideline should be updated (Kendall, 2011) and thus the "NICE Clinical Guideline 82 – Schizophrenia: Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care – update to NICE Clinical Guideline 1" was born. (National Collaborating Centre for Mental Health (Great Britain), National Institute for Health and Clinical Excellence (Great Britain), 2010). This time, the Guideline incorporated principles of patient-centred care - and the prescribing advice no longer advocated atypical antipsychotics. The pharmacological intervention recommendation was to "offer oral antipsychotic medication" in a shared decision-making process, where the healthcare professional informs the service user on the "benefits and side-effect profile of each drug".

A further review was undertaken in 2014 and Clinical Guideline 178 "Psychosis and schizophrenia in adults: prevention and management" (NICE, 2014) incorporated new research evidence and *replaced* the previous CG 82. The new Guideline has a distinctly different tone and emphasizes that treatment should be based on "individual needs and preferences" – with a detailed and prescriptive account of all information that should be presented to the service user to facilitate a meaningful contribution to the decision-making process.

It was expected that prescribing practice would follow the change in evidence and Guidelines, but anecdotal evidence was pointing in the opposite direction. In fact, a substantial rise in atypical antipsychotic prescribing was not justified if the Guideline

implementation process would have been successful. A second step of this study was therefore to conduct a systematic review of published literature relating to antipsychotic prescribing practices, followed by a quantitative analysis of the prescribing data – to establish whether this *anecdotal evidence* is confirmed by factual data. The literature review focused on the prescribing patterns before and after the first and second NICE Guideline with a view to explore whether this pattern changes to reflect the change in recommendations – and explored NICE implementation uptake reports as well as publications discussing pharmacological interventions in schizophrenia generally, or antipsychotic medication prescribing specifically. The quantitative element of this part of the study tracked the prescribing patterns for antipsychotics in England and Wales between 2001 and 2014 using data published by NHS Informatics, the Prescription Cost Analysis data, the National Audit on Antipsychotic Prescribing data, – as well as secondary data from other publications.
If the prescribing practice had followed the research evidence and the guidelines recommendations the data would be expected to show an increase in atypical antipsychotic prescribing after the issue of the first NICE guideline and a subsequent decrease following the published evidence up to 2007 and the guideline revision in 2009. The data in fact showed that this was not the case and a continuous rise in atypical antipsychotic prescribing was identified (from 21 % of total antipsychotic prescribing in 2001 to 66% in 2006 and 81.47% at the end of 2014) – which supports a hypothesis that research evidence is not fully utilised and guideline implementation strategies have not been effective – and therefore other factors are involved in decision making that influence the use of evidence component of the EBM model.

The subsequent part of this study was conducted to investigate this hypothesis. To set this in context it was necessary first to explore the meaning and ‘direction of travel’ of

Evidence Based Medicine (EBM) as the backbone of clinical practice - and the process of guideline implementation as a particular contributor to practicing EBM. The theories of EBM and knowledge transfer may help explain the relationship between evidence, clinical guidelines and clinical practice. This gave the necessary background to the qualitative study exploring with clinicians the array of factors that influenced their prescribing practice.

The study entailed semi-structured interviews in a think-aloud context using a 'hypothetical patient' vignette, indicative of schizophrenia. A purposive sampling method was employed (clinicians with experience in prescribing for schizophrenia, /adult acute psychiatrists and nurse prescribers) and Thematic Analysis (Braun & Clarke, 2006) was used to analyse the in-depth data. A number of themes were identified that revolved around the process of information synthesis and approach to risk, ownership of the decision-making process and collaboration with other influencers, patient involvement and compromise, experience and integration of research evidence – and coalesced around specific typologies of decision-making. The themes mapped on behavioural typologies previously described as 'neuroscience segmentation' and used by pharmaceutical industry to target its drug marketing (Spielmans, 2009), and although some of these components were already known from published literature, the study brought a novel element by highlighting the way in which these factors combine and influence each other, and the varying degree of importance of each factor for individual 'actors'. For example, attitude to risk determines whether the clinician's initial reaction is to treat the symptom or gather more information until a diagnosis is reached. Clinicians who treat symptoms tend to focus on obtaining clinical efficacy, whist clinicians who are more risk averse focus the treatment on minimising the impact of side-effects. More importantly, the way in which research evidence and patient specific factors are utilised varies in each typology, and so do the attitudes and beliefs that shape clinical experience.

The next question was whether the hypothesis of different typologies identified in the qualitative study could be tested quantitatively, to ensure a certain degree of generalisability, and thus to ascertain whether the information derived from the themes can be used in a knowledge translation strategy that makes better use of the understanding we have on how clinician and patient specific factors impact on decision-making beyond the EBM framework. To test the validity of the typologies and determine the weight attributed by each 'type' to specific subjective norms and summative factors, the study used a Theory of Planned Behaviour construct. TBP is a psychological model of behavioural change which can be used to investigate attitudes and beliefs as determinants of behaviour (Ajzen, 1991). A TPB questionnaire was constructed using elements identified in the thematic analysis and following the Manual for Constructing Questionnaires based on TPB (Francis et al., 2004). The questionnaire was then disseminated UK wide to psychiatrists with experience in prescribing or schizophrenia. Although the data was potentially insufficient to draw a substantive conclusion it provides a strong scope for behavioural theories to be integrated in knowledge translation and implementation.

The final chapter is a critical reflection on this body of work and an analysis of its potential impact; it explores whether the findings can be used to identify better methods of cascading evidence in an effective way, focusing on whether an analysis of 'evidence utilisation' patterns should form an integral part of the implementation process.

Epistemic Contextualism: the theoretical lens for this study

The thesis follows a theoretical lens of epistemological contextualism. This philosophical stream of thought postulates that "knowledge" has a number of fundamental characteristics which can be captured by a reductive definition: there are some conditions both necessary and sufficient for the definition to be true.

For example, when we think about 'knowledge', particularly in a scientific context we expect that it has certain characteristics, such as justification, or reliability through replicability. However, there are contextual parameters to these characteristics, and Baumann (2016) argues that epistemic standards are only one type of parameter, and introduces a distinction between standards, depending on the subject's own epistemic position, on their determination of what needs to be ruled out, on the evidence the subject has on the matter, on the reliability of their beliefs, and on the subject's required degree of belief.

In plain terms, what we think 'we know' depends entirely on the context, and 'knowledge' is context sensitive: it can only fulfil it's necessary and sufficient attributes in a specific context. What is different in each context is how well-positioned a subject relative to the matter to count as "knowing" it.

In the natural world in fact we all contextualise knowledge and refute blanket statements: if David's height is 6ft 2in we can say we 'know' that David is tall. This statement fulfils the 'necessary and sufficient' criteria of justifiability and reliability, such as average height of a mature Caucasian human male is 5ft 10in. However, statements such as "David is tall" can only be true if David is placed in a group of people of average height: if David were to stand in a group of people whose average height is over 6ft 5in, then the statement does not hold., as David is no longer tall (in relation to the context). It is therefore logical that 'knowledge of something' is a contextual concept.

This theoretical lens provides a useful context for the investigation of what we hold to be 'knowledge' and 'evidence' - as they are created and summarised in a restricted contextual framework, as the thesis will demonstrate when discussing the way in which the definitions and categorisation of schizophrenia has changed, the shift in what constitutes *necessary and sufficient* criteria of 'evidence' and the context in which evidence is summarised to produce guidelines or recommendations.

Epistemic contextualism postulates that knowledge attribution (our knowledge of the 'facts') depends on the context of 'the attributor'. This standpoint recognises that the 'attributor's own stake, position and/or scepticism about the 'fact' influences the way in which 'knowledge' is created. Thus, 'contextualism' is used to refer to an alternative perspective to 'epistemic realism'. Realism assumes that 'knowledge' and 'beliefs' have an underlying "structural unity" that makes them all *"instances of a particular kind"* independent of any *"situational, disciplinary and other contextually variable factors"* (Williams, 1991 p. 119)

By contrast, 'contextualism' as in the views of Popper (9179) and Wittgenstein (1953), maintains that any proposition about 'knowledge' has epistemic value only in relation to the situational factors.

Contemporary interpretations of epistemic contextualism's role in debating mental health and illness originate in Foucault's primary thesis in *Folie et déraison: Histoire de la folie à l'âge Classique (Madness and Insanity: History of Madness in the Classical Age),* which traces the evolution of the concept of madness from Renaissance to the modern experience and advances the idea that the way in which society has dealt with 'madness' is a social construct quite distinct from mental illness (Foucault, 1961). Foucault's greatest insight is that the whilst in Renaissance 'the mad' are integral to the fabric of society (and viewed as an illustration of the distinction between what men are and what they pretend to be) – in the later classical age (17th and 18th centuries) the asylum is born from an effort to normalize

behaviour to conform to bourgeois ideals: ‘the mad’ are to be isolated and confined, in a “juridical space” - not of treatment, but for social control. The outcome is to segregate and “silence” madness, away from society.

The idea that a historical perspective is a useful point of view in developing our understanding on how context shapes knowledge and action is also employed in a beautiful exploration of the manifestations and meanings attributed to madness: Scull’s Madness in Civilization (2015) expands on the contextual influences on our understanding of irrational and psychotic behaviour and our varied responses to it by constructing psychological or social explanations in an effort to *“tame the demons of unreason”* – and illustrates how societal context shaped the construct of a distinction between the mind and the brain.

Scull supports the idea that *“the brain’s very structure and function are a product of the social environment. […] Somewhere in that murky mix of biology and the social lie the roots of madness”*

In this context, it is appropriate to use epistemological contextualism as a lens to explore the changes in the label of ‘schizophrenia’. Given the wide variety of symptoms, trajectories and outcomes, an analysis of the concept could not be anchored in ‘realism’, as there is no inherent “structural unity’; this is also valid for the analysis of the way in which the diagnostic criteria have changed from a categorical to a dimensional approach.

Moreover, this perspective provides as useful framework of reference for understanding the medical model and reliance on psychopharmacology to control the socially undesirable behaviours: recent trends in critical psychiatry return to Szasz’s view that schizophrenia is a social construct [umbrella] term applied indiscriminately to medicalise a set of behaviours (Szasz, 1988)

Furthermore, this s an appropriate lens to reflect on how the role of ‘evidence’ in medical practice has changed: the whole tenet of EBM is a contextual matter: its roots set the criteria for evaluating evidence of effectiveness and efficacy, and its epidemiological method for the practice of medicine is a guide to integrating aforementioned evidence into a patient-level decision.

Last but not least, epistemic contextualism serves as an ideal perspective from which to explore whether the Theory of Planned Behaviour may be used to determine whether the subject’s own epistemic position and the reliability of their beliefs could be used in knowledge translation and implementation.

Chapter I

Setting the scene: background considerations supporting the research hypothesis

The purpose of this introductory chapter is to give a context to the investigation (the nature of the problem), present the background of the research question (why is this important), and a review of the literature that framed the exploration (what we know about this problem) – essentially to justify this research and introduce key concepts. It also aims to provide a theoretical reference framework that was used to integrate the hypothesis.

The chapter will briefly map the evolution of the definition of schizophrenia as a concept, in particular the differences between categorical and dimensional approaches - as it influences the diagnostic and therapeutic options - and will review the current pharmacological interventions. Then, it will explore the use of 'evidence' in the guideline development process and establish how this contributes to practicing Evidence based Medicine.

The exploration showed that an apparent contradiction exists between the tenets of Evidence Based Medicine (EMB) and the actual clinical-decision making process, as ultimately the result tends to be a therapeutic decision that does not always comply with the guideline-endorsed practice. This raised the question on whether the evidence (E in EBM) is not reliable, whether EBM as a concept is 'broken', or the knowledge translation and implementation framework on which this process depends was not based on realist synthesis and therefore does not map on real-world practice.

A few interesting serendipitous findings prompted speculation on whether a rigid interpretation of 'evidence' is applicable at all to psychiatry. This is based on the acknowledgement that a number of influences shape current scientific and social construct of

mental health conditions in general and schizophrenia in particular. In no particular hierarchical order of importance or weigh of influence, the following factors must be acknowledged as main contributors to the way in which the conceptualization, diagnostic and treatment of schizophrenia is built:

a) the continued search for a biological, organic, genetic or molecular cause for schizophrenia that expands beyond the dopamine hypothesis; this anchors the view that schizophrenia is a 'disease' whose treatment can be approached as all other somatic diseases and supports the duality of mind and brain.

b) the increased medicalisation of behaviors deemed to be socially unacceptable – in this case the behavioral consequences of the positive and negative symptoms of schizophrenia. This influence stems from a variety of sources: the general public's view that normal psychological states (such as low mood or anxiety) no longer require developing a coping mechanism and can be instead 'eradicated' by medication; the influence of marketing strategies by pharmaceutical industry in search of new conditions for which 'old' compounds can be marketed; and last but not least, the academic debate between biological and psychological etiology of mental health conditions and the influence of either explanation on stigma associated with mental illness.

c) an evolving definition of what constitutes 'schizophrenia', what diagnostic factors sum up the symptoms and the transition from a categorical to a dimensional approach in the formal diagnosis of the condition and outcome prognosis.

d) an evolving model of medical care, with the requirement to base treatment decisions on research evidence, clinical expertise and patient's views (the Evidence Based Medicine model) – and in this context a continuously evolving social construct of what constitutes 'evidence' (and how value/strength is to be ascribed to evidence) - as well as the emergence

of the idea that healthcare is co-produced between the healthcare provider, the clinician and the patient.

These factors are some of the important contributors to the way in which treatment of schizophrenia is explored in this thesis and are the basis in which the research question is framed.

An evolving definition of schizophrenia and treatment options

"many of psychiatry's disease concepts today are merely working hypotheses and their diagnostic criteria are provisional" (Jablensky, 2013)

The ambiguous aetiology, pathophysiology and psychopathology of schizophrenia has led to a variety of diagnostic subtypes that have been reshaped and redefined over the last century and certainly with each iteration of psychiatry textbooks, diagnostic and coding manuals. The heterogeneity of its clinical manifestations has given rise to a variety of ontological framings, from a rejection of its very existence as a distinct condition (Geekie & Read, 2009; Henderson & Malhi, 2014; Lasalvia, Penta, Sartorius, & Henderson, 2015; Os, 2016) to an elaborate construct of symptoms. For the purpose of this thesis, the definitions discussed here do not aim to be an extensive historical account of its construct from its Kraepelian roots and the Schneiderian nosology of psychoses to its current working definition, neither a guide to diagnosing schizophrenia. The aim of this chapter is focus on the changes contemporaneous with the time-frame relevant to this study, and on the transition from categorical approaches to dimensional approaches in diagnosing and manging schizophrenia, to outline the concepts that may influence clinicians' own views on the subject.

Schizophrenia is defined by World Health Organisation as *"a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self […] includes psychotic experiences, such as hearing voices or delusions […] can impair functioning through the loss of an acquired capability*" (Costa E Silva, 1998). This definition, notwithstanding the deliberate ambiguity of its terms, mirrors the WHO's International Statistical Classification of Diseases and Related Health Problems (ICD) and earlier versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM).

The ontological roots are very clearly apparent in this definition, and as a matter of fact in all definitions as they evolved in the DSM and can be closely mapped on historical developments of the concept: the avolition/anhedonia, dissociative pathology other negative symptoms, as well as the expected poor functional outcome, can be dated back to Bleuler and Kraepelin - whilst the incorporation of positive symptoms and the accent on reality distortion is clearly of Schneiderian influence.

The prevalence of each perspective though has varied throughout the evolution of the definition (Bruijnzeel & Tandon, 2011; Keller, Fischer, & Carpenter Jr., 2011; Tandon, Bruijnzeel, & Rankupalli, 2013): earlier versions of DSM (I and II) focused more on negative symptoms and the impact on social functioning, whilst DSM–III (3rd ed.; DSM–III; American Psychiatric Association, 1980) added a prerequisite of chronicity and became a paradigm-changer by emphasising "first-rank" symptoms (Wilson, 1993). No major change was introduced by the revised edition (3rd ed., rev.; DSM–III–R; American Psychiatric Association, 1987) apart from the removal of the age of 45 to onset criteria and the addition of very useful operational criteria (Keshavan, 2013) – but the historical evolution perspective in developing the 'construct of schizophrenia' is relevant in the context of both diagnosis and treatment. Building on earlier works by Hughlings Jackson, and differentiating between positive and negative symptoms was a turning point for the way in which schizophrenia was conceptualised (Pearce, 2004). This enabled psychiatry to postulate a new thesis of distinct pathophysiology for the positive and the negative symptoms (Strauss, Carpenter, & Bartko, 1974), and paved the way for 'multiple symptom domains' in describing and categorising the condition.

This seems to have been only the beginning of a spiralling effort to delineate the features for each of the symptoms and the sub-typing which characterises DSM-IV (4th ed.; DSM–IV; American Psychiatric Association, 1994) and DMS-IV-TR (4th ed., text rev.;

DSM–IV–TR; American Psychiatric Association, 2000), and extensive work has been directed towards identifying scientific validity and practical reliability (Andreasen & Olsen, 1982). The construct of 'schizophrenia' in DSM-IV and DSM-IV-TR is largely considered to be supported by predictive validators in terms of diagnostic stability (Haahr et al., 2008) and treatment response (Korver-Nieberg, Quee, Boos, Simons, et al., 2011) but the majority of sub-types listed in DSM-IV were not very successful in accounting for the heterogeneity of schizophrenia and had no apparent clinically significant utility as they could not be considered stable conditions (Tandon, Gaebel, et al., 2013) – and were subsequently removed in DSM-5 (American Psychiatric Association, 2013; Anna, Ehret, Ehret, & Berking, 2013)

The limitations stemming from the categorial approach revolve around homogeneity: the division of disorders into classes based on defining features works well for mutually exclusive categories, with clear demarcation lines, and where all the 'members' of this class have consistently the same features. Two individuals diagnosed with schizophrenia will have quite different symptoms and severity of symptoms, and a categorical approach will not allow to differentiate between different aetiologies, age, gender, cultural background, etc – which may alter the interpretation of negative symptoms in particular. APA acknowledges this limitation and cautions that *"…there is also no assumption that all individuals described as having the same mental disorder are alike in all important ways. The clinician using DSM-IV should therefore consider that individuals sharing a diagnosis are likely to be heterogeneous even in regard to the defining features of the diagnosis and that boundary cases will be difficult to diagnose in any but a probabilistic fashion"* (American Psychiatric Association, 2000) – and several authors highlight that this may lead to artificially diagnosed comorbidities (Bottas, Cooke, & Richter, 2005; Cunill, Castells, & Simeon, 2009; Maj, 2005; Spitzer & Wakefield, 1999)

On the other hand, albeit dimensional approaches allow the development of 'profile' from symptoms and acknowledge causal contributors, a number of limitations have been identified in operationalising the concepts. Managing scores across dimensional constructs may raise difficulties for clinicians and decrease the acceptability of dimensional approaches. (First, 2005)

The diagnostic convention based on the subjective interpretation of a specific number of self-reported symptoms and deteriorating social performance stipulated by DSM-IV has been replaced by a dimensional method of assessing clinical symptoms in DSM-5 and were deemed to be of significance beyond taxonomy.

Whilst the DSM-IV category was called "Schizophrenia and Other Psychotic Disorders", in DSM-5 it has been re-named "Schizophrenia Spectrum and Other Psychotic Disorders" (5th ed.; DSM-5; American Psychiatric Association, 2013) and simply by adding the word 'spectrum' to the label places schizophrenia in different context, highlighting that a patient may fall anywhere on a continuum rather than in a specific category. This is supported by new knowledge on the nature of the condition and, in turn, opens a whole new avenue to future research on treatment options. The clarification of course specifiers (both longitudinal an cross-sectional) and the demarcation of treatment-relevant psychopathological dimensions, acknowledges the multi-dimensional nature of the psychotic disorders (Carpenter & Tandon, 2013) and is expected to improve accuracy of measurement-based diagnosis and treatment. (Tandon, Gaebel, et al., 2013)

In the dimensional approach, the heterogeneity of symptoms are not clustered across sub-types, but in distinct symptom domains: reality distortion (with delusions and hallucinations as items), negative symptoms, disorganization, cognitive impairment, motor symptoms, and mood symptoms (with depression and mania as items) and the severity of each of these items can be measured on a 0-4 rating scale – as an indicator of potential individualised treatment

options and measurement of disease progression and treatment response. (Barch et al., 2013; Heckers et al., 2013; Tandon, 2016)

> *"You have symptoms of psychosis and mania, and we classify that as schizoaffective disorder. If your psychotic symptoms disappear we may reclassify it as bipolar disorder. If, on the other hand, your mania symptoms disappear and your psychosis becomes chronic, we may re-diagnose it as schizophrenia.*(van Os, 2016)

The relevance of this approach consists in the acknowledgement that categorisation will not inherently equate to diagnoses of distinct conditions - but merely describes a cluster of symptoms. Os (2016) proposes that, given the heterogeneity in psychopathology and response to treatment this should be re-labelled 'psychosis spectrum syndrome' with schizophrenia at the least favourable outcome end of the spectrum.

This view is supported by earlier research, which highlighted that confines of categorical entities may not be as definite as suggested by original definitions and what was labelled as co-morbidity associated to a condition may very well in fact be an impairment of other dimensions of cognition and other neurobiological functions[1]. (Owen, Craddock, & Jablensky, 2007; Perlstein, Dixit, Carter, Noll, & Cohen, 2003).

The framework for 'deconstructed' schizophrenia was introduced by Strauss (1974) who provided empirical evidence for three domains: psychotic, negative and disorganisational symptoms (Strauss, 2014; Strauss et al., 1974) and elaborated later on by Peralta & Cuesta (2001) in a synthesis of major studies on the factor structure of symptoms, which identified eight major dimensions of psychopathology (with mania, depression, excitement, catatonia

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[1] Kraepelin himself acknowledged that the dichotomous formulation may be incorrect and three syndromes aggregated as *dementia praecox* (hebephrenia, catatonia and paranoid dementia) is a cluster of 'amassed' clinical presentations which *"do not represent the expression of particular pathological processes, but rather indicate the areas of our personality in which these processes unfold"* (Kendler & Jablensky, 2011)

and lack of insight added to the previous three) and proposed a hierarchical approach based on levels of complexity – with, most notably, a highlight that they are not unique to schizophrenia but shared among psychoses and should therefore be considered dimensions of psychosis rather than of schizophrenia alone. (Peralta & Cuesta, 2001).

Including a dimensional assessment of main symptoms of psychotic disorders intrinsically acknowledges variability and theoretically could dispense with categorical denomination, but in practice dimensional approaches are often 'translated' into (or at least informed by categorical approaches - by using validated scales and instruments to score the severity of a symptom below or above a clinically significant cut-off point.

Indeed, the argument between categorical and dimensional approaches is not at ontological level but rather related to its clinical utility: the authors of the diagnostic manual highlight in its introduction that its primary intended use is to guide clinical practice (with secondary purposes such as framing future research and educating practitioners and "the public" about psychopathology equally important). It specifically mentions that criteria sets for schizophrenia (and other disorders) were added because their implications for clinical practice, and treatment selection in particular, outlining that certain specifiers are predictors of outcome. This is a powerful argument in favour of a dimensional approach and the implications for treatment are substantial, if the presence of absence of particular specifier, or a particular score on this specifier's rating scale is not only a diagnostic tool but also a predictor of poor treatment response, and if severity of symptoms and their progress over time can be quantified to inform the care pathway and future treatment requirements.

It also brings psychiatric assessments seemingly closer to somatic medicine and this puts the Evidence Based practice in psychiatry in a whole new light, if there is a baseline acknowledgement that the type and severity symptoms varies across patients, and over time quantifiably within individual presentations, then establishing the initial treatment plan and

mapping the response to treatment over time has more than the basic tenets of EBM to consider and makes a significant move toward Person-Centred Care. The ability to quantify the severity of each 'symptom dimension' yields useful clinical information about the nature of the illness in "this particular patient"; the impact of the treatment can be measured by looking at the progression of each symptom and this can then be discussed with the patient in a co-production format. The patient can meaningfully contribute to shaping the treatment plan based on their own views on the severity and impact of each symptoms and expectations on progress and therefore the outcome can be better informed and managed. The 'readily available' simple Clinician-Rated Dimensions of Psychosis Symptom Severity rating scale is not expected to necessarily replace other validated symptom rating scales such as the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), or Scale for the Assessment of Negative Symptoms (SANS) nor the global measures of severity such as the Clinical Global Impression-Change (CGI-C) or the Global Assessment of Function scale (GAF) but it establishes a score profile rather than relying on a combined score and provides possibly a more coherent view on the relationship between the measures and the specific symptom dimensions. The implications are that 'individualised', differentiated and specific treatment is possible and enable to 'break down' the problem in its's component entities: positive symptoms and disorganisation can be managed by dose titration or switching to another class of antipsychotics, secondary negative symptoms and cognitive deficits can be managed based on the clinical outcomes and other symptoms that persist and are deemed important by the patient (such as depression or anxiety) can be managed by discussing with the patient their expectations in relation to treatment response (Tandon, 2016)

Published literature features both pro and contra arguments for the dimensional approach in terms of their clinical utility, and this may have an impact on its implementation.

Arguments supporting the dimensional approach revolve around the identification of diagnostic comorbidity as an 'artefact' of the categorical approach (First, 2005) and the need to a) replace the DSM IV typologies and classification so that disorders with the same underlying dimension are placed in the same group, b) provide empirical evidence to support clear boundaries in the distribution of symptoms across sub-types and between conditions, and replace arbitrary diagnostic thresholds – and c) the need for better ways to ensure diagnostic stability over time.

Widiger & Samuel (2005) highlight that the categorical model has a great number diagnostic co-occurrences and no clear demarcation between symptom severity in each category, which led to an overuse of 'not otherwise specified' categories to diagnose conditions that do not fall strictly into one of the categorical markings (Widiger & Samuel, 2005). Watson (2003) argues that some diagnostic groupings are not supported by empirical data that reflects common comorbidities across disorders, and Krueger (2005) adds that common co-occurrence of some symptoms may be part of an externalising dimension and therefore are likely to share a common pathophysiology.(Krueger, Markon, Patrick, & Iacono, 2005).

The arguments rejecting the dimensional model fall into two categories: the first one debating the utility in clinical practice of the model itself, and a second category debating the process of change, the utility of a radically overhauled approach and user acceptability. Main concerns have been reported around clinical assessment and the ability to evaluate a patient using a categorical system by mapping the extent o to which the presentation matches a diagnostic category: diagnostic criteria are not assessed individually at every evaluation, whilst with a dimensional approach, a diagnostic assessment requires an evaluation of the

severity score for each dimension – which can be time consuming and were not routinely part of clinical practice. (Widiger & Simonsen, 2005)

Communication with colleagues and other clinical teams is also mentioned: conveying a diagnostic is easier when a categorical approach is used; describing the patient in terms of scores of several dimensions may be more precise but potentially of limited clinical utility to clinicians who routinely think of treatment in terms of categories of mental disorder. (Mullins-Sweatt & Lengel, 2012).

The 'disruption' to clinical practice and a need to re-train clinicians unfamiliar with the dimensional approaches has been cited. As changes made to DSM up to DSM 5 have been mainly refinements and incremental improvements, to which clinical practice adapted, the adoption of a dimensional approach also entails an additional administrative burden by complicating medical record keeping and reporting. First (2005) points out that, as it no longer maps on ICD classifications, a dimensional model for mental disorders used in parallel to a categorical model for medical conditions creates a "barrier between mental disorders and medical conditions and between mental health professionals and medical practitioners, reinforcing widely held prejudices that mental disorders and medical conditions are somehow fundamentally different" (First, 2005)

Other arguments mention the impact on research (Tandon, Gaebel, et al., 2013), in particular the ability to synthesize evidence across studies in meta-analyses, as diagnostic inclusion criteria would have been different – but also the ability to conduct longitudinal studies when the patient population has been diagnosed at onset using a categorical approach and treatment response evaluated on a different scale. This has important implication for the purpose of this study as it essentially means that integrating the dimensional approach to diagnosis and treatment of schizophrenia complicates clinicians' efforts to integrate prior clinical research

based on the categorical approach, and it is one of the criteria to be considered when discussing knowledge utilisation patterns.

Irrespective whether an individual clinician is a proponent of the categorical or the dimensional approach, it is expected that he/she will have a robust knowledge of the treatment options available. Antipsychotics are the basis of the pharmacological interventions in schizophrenia, but they have a selective action on different psychopathological domains. Positive symptoms and disorganisation are generally regarded as susceptible to improvement with antipsychotic treatment, whilst negative symptoms will probably not show a treatment response; mood and motor symptoms have shown a variable response (Tandon, 2016). Even if various symptoms or symptom dimensions are relatively independent, they do tend to co-vary in the course of treatment (Tapp et al., 2013) with both typical and atypical antipsychotics.

The next part of this chapter will review briefly the available pharmacological treatment options for diagnosed schizophrenia. Similar to the review of the evolution of schizophrenia as a concept, the review of antipsychotics below aims only to set the context and present the treatment options available, and is not an exhaustive review of the pharmacodynamic and pharmacokinetics of each class of drug. The evidence-base for the safety and efficacy of different classes of antipsychotics is reviewed to map the change in evidence that resulted in a change in the Clinical Guideline.

Table 1.

Categoric Diagnostic criteria for Schizophrenia as per the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV

A. Characteristic symptoms	B. Social/Occupational Dysfunction	C. Duration	D. Schizoaffective and Mood Disorder exclusion:	E. Substance /general medical condition exclusion:	F. Relationship to a Developmental Disorder:
Two (or more) symptoms, for at least 1 month (1) delusions (2) hallucinations (3) disorganized speech (4) disorganized or catatonic behaviour (5) negative symptoms Only one symptom required if delusions are bizarre	One (or more) major areas of functioning (work, relations / self-care) for significant portion of time markedly below the level achieved prior to the onset	Continuous signs of disturbance for at least 6 months, and include at least 1 month of Criterion A symptoms	No major Depressive episode or Manic episode occurred concurrently with the symptoms	Not due to the direct physiological effects of a substance or a general medical condition.	The additional diagnosis of Schizophrenia made only if prominent delusions /hallucinations are also present

Note: Adapted from *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.), American Psychiatric Association. (2000). doi:10.1176/appi.books.9780890423349, CC BY-NC

Table 2.

Dimensional assessment of symptoms and related clinical phenomena as per the Diagnostic and Statistical Manual of Mental Disorders (DSM)5

	0	1 Equivocal	2 Present /Mild	3 Present /Moderate	4 Present / Severe
Hallucinations	Not present	Severity / duration not sufficient to be considered psychosis	Little pressure to act upon voices, not very bothered by voices	Some pressure to respond to voices / somewhat bothered by voices	Severe pressure to respond to voices / very bothered by voices
Delusions	Not present	Severity /duration not sufficient to be considered psychosis	Delusions not bizarre / little pressure to act / not very bothered by beliefs	Some pressure to act upon beliefs / somewhat bothered by beliefs	Severe pressure to act upon beliefs / very bothered by beliefs
Disorganized speech	Not present	Severity / duration not sufficient	Some difficulty following speech	Speech often difficult to follow	Speech almost impossible to follow
Abnormal psychomotor behavior	Not present	Severity /duration not sufficient to be considered abnormal	Occasional abnormal /bizarre motor behavior /catatonia	Frequent abnormal /bizarre motor behavior / catatonia	Constant abnormal / bizarre motor behavior / catatonia
Negative symptoms	Not present	Decrease in facial expressivity / prosody	Mild decrease in facial expressivity / prosody	Moderate decrease in facial expressivity / prosody	Severe decrease in facial expressivity / prosody
Impaired cognition	Not present	Cognitive function not clearly outside the range expected for age	Some reduction in cognitive function below expected for age	Clear reduction in cognitive function	Severe reduction in cognitive function
Depression	Not present	Occasionally feels sad, depressed or hopeless; concerned but not preoccupied	Frequent periods of feeling sad, moderately depressed; concerned, with some preoccupation	Frequent periods of deep depression / hopelessness; preoccupation with guilt	Deeply depressed /hopeless daily; delusional guilt / unreasonable self-reproach
Mania	Not present	Occasional elevated, expansive / irritable mood / some restlessness	Frequent periods of somewhat elevated, expansive / irritable mood / restlessness	Frequent periods of extensively elevated, expansive / irritable mood / restlessness	Daily and extensively elevated, expansive / irritable mood / restlessness

Note: Adapted from Logic and justification for dimensional assessment of symptoms and related clinical phenomena in psychosis: Relevance to DSM-5, by Barch, D.M., et al., (2013), *Schizophr. Res.,* http://dx.doi.org/10.1016/j.schres.2013.04.027

In parallel to the changes in the way schizophrenia is defined and diagnosed, the treatment options have also evolved, albeit not necessarily contemporaneous with the change in the diagnostic manual.

The general mode of action of antipsychotics is either increasing or decreasing the activity of neurotransmitters. Inhibitory neurotransmitters (monoamines, such as serotonin) decrease the action response potential of the receptor, whilst conversely excitatory neurotransmitters (such as noradrenaline) increase it. Modulators (such as dopamine, and acetylcholine) will generate either an inhibitory or an excitatory effect depending on the receptors present. Antipsychotic agents will change the effects of neurotransmitters: agonists will increase the effects of specific neurotransmitters, whilst antagonists will block the effects of neurotransmission. They do this by either mimicking what the neurotransmitters do (direct effect) or by acting on the synaptic receptors (indirect effect).

In addition to their pharmacological classification, antipsychotics can be classified by their chemical structure and by their clinical properties.

The first antipsychotic agents (haloperidol, chlorpromazine and trifluoperazine) - now referred to as ‘first generation antipsychotics’ - appeared in 1950s and their main mechanism of action was reducing the effect of dopamine, by blocking the D_2 dopamine receptors. They are however not selective for any of the four dopamine pathways in the brain and therefore will cause a range of extrapyramidal side-effects symptoms (such as tardive dyskinesia and akathisia) and will raise serum prolactin levels. Some of the phenothiazines (such as chlorpromazine) have a pronounced sedative effect and moderate extrapyramidal side-effects, whist others (such as fluphenazine and trifluoperazine) and butyrophenones (such as haloperidol) will have fewer sedative and antimuscarinic effects but more pronounced extrapyramidal side-effects. Thioxanthenes (flupentixol and zuclopenthixol) have moderate sedative and extrapyramidal effects.

The second-generation antipsychotics, first developed in the 1970s (and a new wave in the 1990s), act on a range of receptors and have distinct clinical properties, particularly in relation to side-effects. The theory is that whilst first generation antipsychotics bind to the D_2 receptor more tightly than dopamine itself and the dissociation time-course is slower than that of dopamine, the second generation drugs occupy D_2 receptors only transiently and dissociate rapidly to allow normal dopamine neurotransmission, and also block the serotonin receptor 5-HT_{2A} receptors at the same time - which confers the atypicality label (Seeman, 2004). The need for a new class of drug was borne out of the need to mitigate the extrapyramidal side-effects (EPS) of the first-generation drugs (known henceforth as 'typical antipsychotics') and the 'fast-off' dopamine receptor dissociation and 5-HT_{2A} antagonisms prevents EPS, keeps cognition levels intact, and prolactin levels normal – in brief eliminates all the undesired side-effects of the typicals.[2] There is however a new type of side-effects, more difficult to control and with longer ranging impact: atypicals can cause metabolic side-effects (hyperglycaemia, diabetes, weight gain ironically is caused by the agent that solved the problem, as the α_1 adrenoceptor and 5-HT_{2A} receptor have a fundamental role), a clear increase in the risk of stroke and other cardiovascular events (Kabinoff, Toalson, Masur Healey, McGuire, & Hay, 2003) and is associated with increased mortality in elderly patients with dementia (Gill, Bronskill, Normand, & al, 2007; Schneeweiss, Setoguchi, Brookhart, Dormuth, & Wang, 2007).

[2] This is in fact not true for all the second generation drugs: for instance Amisulpride is a benzamide, so it may cause hyperprolactinaemia and EPS side-effects. This may be less common as it blocks the mesolimbic pathway to a greater extent than the striatal pathway, but the dopaminergic blockade causes a homeostatic 'supersensitivity' response in the striatal pathway, with effects on the cholinergic, GABAergic and glutaminergic triangle (Carlsson & Carlsson, 1990)

Table 3.

Comparative efficacy and side-effect profile for some of the most used typical and atypical antipsychotics

Agent	Efficacy		Adverse effects							
	Positive symptoms	Negative symptoms	Anticholinergic	Cardiac repolarisation	Hypotension	Hyper prolactenemia	Type 2 Diabetes	Weight Gain	EPS	NMS
Typicals										
Flupentixol	+++	+	0	0	+	++	+	0	++++	+++
Fluphenazine	+++	+	+	0	+	+	+	++	+++	+++
Haloperidol	+++	+	+	0	+	+	+	++	+++	+++
Trifluoperazine	+++	+	+	0	++	+	+	++	+++	++
Zuclopenthixol	+++	+	++	0	+	++	+	++	+++	++
Chlorpromazine	+++	+	+++	++	+++	++	+	++	++	+
Thioridazine	+++	+	++	++	+++	++	+	+++	+	+
Atypicals										
Amisulpride	+++	+	0	0	+	0	++	0	++	+
Aripiprazole	++	+	0	0	+	0	+	0	+	?
Clozapine	+++	++	+++	0	+++	0	++	+++	0	+
Olanzapine	+++	+	+	0	++	+	++	+++	+	+
Quetiapine	++	+	+	0	++	0	+	++	0	+
Risperidone	+++	+	0	0	+++	++	+	++	++	+
Ziprasidone	+++	+	+	+	+	+	+	+	+	+

Note: Benefit/Risk: 0 negligible/absent; + low/ infrequent; ++ moderate; +++ high/ frequent; ++++ very high: ? poorly defined

Adapted from: 1) Keks, N. A. (2004) Are atypical antipsychotics advantageous? *Australian Prescriber*, *26*(4) © Copyright National Prescribing Service Ltd.- reproduced with permission; and 2) Gardner, D. M., Baldessarini, R. J., & Waraich, P. (2005). Modern antipsychotic drugs: A critical overview *CMAJ*. © Copyright (2005) Canadian Medical Association and the Canadian Medical Association Journal (www.cmaj.ca) and Access Copyright - reproduced with permission

This chapter is not meant to be an exhaustive review of pharmacodynamic and pharmacokinetic properties of antipsychotic agents, but it is helpful to understand how treating one symptom may generate another and why the pharmacological profile of these drugs cannot predict the treatment response. Whilst positive symptoms such as hallucinations and delusions are caused by a hyperactivity in the dopaminergic activity in mesolimbic pathways, antipsychotics are not selective to a particular pathway (Stahl, 2013) and antagonism of D_2 receptors affects the entire dopamine pathway system, with harmful side effects. Paradoxically, reducing the dopaminergic activity in the mesolimbic pathway causes negative symptoms, such as anhedonia; this is important as in the mesocortical pathway endogenous D_2 activity is low anyway (this is the cause for negative symptoms, affective dysregulation and cognition impairments) and therefore administering a pharmacologically indiscriminate antipsychotic further compounds the problem. In ways that have not been fully elucidated by pharmacology, this homeostatic response persists even after the discontinuation of the treatment and they become part of treatment emergent syndromes, where the solution becomes part of the problem. (Healy & Tranter, 1999)

It has been postulated that pharmacology alone will not result in the optimal choice of treatment, and a clinical definition must be informed by physical and behavioural responses of the patient as a whole, not only by his/her neuronal response (Ashton, Young, & Ferrier, 1999). Clinical studies comparing safety and efficacy have shown very little difference in efficacy between each of the antipsychotic drugs (apart from clozapine), and treatment response is variable[3], therefore no one first-line antipsychotic can be deemed suitable for all patients. Choice of medication is influenced by a variety of factors that relate to the condition

[3] A 2013 meta-analysis by Leucht et al. identified small differences in efficacy between 15 different antipsychotics and this includes both typicals and atypicals (Leucht et al., 2013). Authors suggest that the classification by pharmacological properties is no longer relevant and a hierarchy based on efficacy and different side-effect domains would be more useful to the clinician.

itself (such as the potency or degree of sedation required, or the presence of negative symptoms), by the patient's risk factors (such as the propensity to develop metabolic or cardiovascular side-effects) – but also by a whole host of factors relating to the prescriber. To decide on a specific treatment indication for a particular patient, a clinician will rely on his clinical experience and on information available about the safety and efficacy of a specific drug. A brief look at the sources of information on psychosis and schizophrenia that NICE lists on its Evidence webpage returns 482 items of Guidance and Policy (63 items of guidance, 14 items of policy, 61 Quality indicators, 346 Prescribing information), another 378 Secondary Evidence sources (178 systematic reviews, 1 economic evaluation, 133 evidence summaries, 3 Health Technology Assessments and 63 evidence uncertainties) and 284 items of primary research and 6 ongoing trials. It is practically impossible for any individual clinician to keep abreast of such an avalanche of information therefore it is safe to assume that clinicians will look for summative guidance documents to inform their treatment choices. The next chapter is an exploration of the Schizophrenia guidelines and their evolution based on research evidence.

Research evidence and Schizophrenia Guidelines: an exploration of Clinical Guideline development and mapping changes in evidence that led to a change in guideline

This chapter aims to provide contextual information on how developing 'research evidence' relating to the safety and efficacy of various classes of antipsychotics influenced the clinical guideline development, particularly the recommendations related to prescribing. It follows three subsequent iterations of the same guideline and maps out the changes as they emerged in response to the critique of the existing contemporaneous evidence and the evolving new evidence.

The Clinical Guideline 1: NICE or not nice?

> *"The guideline programme developed by the National Collaborating Centre for Mental (NCCMH) Health for the National Institute of Health and Clinical Excellence (NICE) is probably the most comprehensive and methodologically advanced mental health guideline programme in the world"* (Kendall, Glover, Taylor, & Pilling, 2011)

The National Institute for Health and Clinical Excellence (NICE) was set up in 1999 with the specific aim of producing evidence-based guidance to reduce the discrepancies and local variation in the treatments offered by the NHS, to *"resolve uncertainty about which medicines, treatments, procedures and devices represent the best quality care and which offer the best value for money for the NHS"*, as well as a range of public health guidance to encourage *"healthy living, promote wellbeing and prevent disease"* (NICE mission statement, 2011)

The implementation of guidance issued by NICE was meant to be built in the National Service Framework for England and Wales and form integral part of the Service Development Plans. Compliance with the NICE Clinical Guidelines and Technology Appraisals has been identified as a 'key target' for improvement in Health Services.

The very first Clinical Guideline developed by the National Collaborating Centre for Mental Health was on Schizophrenia: "Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care. NICE clinical guideline 1" (National Institute for Health and Clinical Excellence, 2002)

The fact that the first clinical guideline to be produced by NICE was a mental health guideline and specifically providing advice and guidance to the NHS regarding the treatment of schizophrenia – the most severe manifestation of mental illness – has had a significant impact on how this guidance was perceived. The stakeholders from the medical and academic community as well as service-user groups were not fully conversant with the policy background, the way in which the guidelines were compiled and the detailed evaluation of evidence which formed that basis of the guideline – nor with the way in which this guideline would integrate with the plethora of other national and regional initiatives.

As members of the Guideline Development Group (GDG) Kendall and Pilling were best placed to shed light on the some of these issues. In a series of articles (Kendall, Pilling, Pettinari, & Whittington, 2004; Kendall, Pilling, Whittington, Pettinari, & Burbeck, 2005; Pilling & Price, 2006) sought to clarify the position and role of the National Collaborating Centre for Mental Health, the Guideline development process (including the role of the GDG) and provide a detailed explanation of the methods employed in searching for the evidence, analysing the evidence and the process of developing evidence statements.

A five-step process is described by Pilling & Price (2006) "*1. Define the clinical questions focused on key areas of clinical uncertainty. 2. Develop and implement appropriate search*

strategies. 3. Design protocols for the evaluation of the evidence identified. 4. Synthesise and (meta-) analyse the evidence, guided by the clinical questions. 5. Generate summaries of the evidence and develop the recommendations for clinical practice".

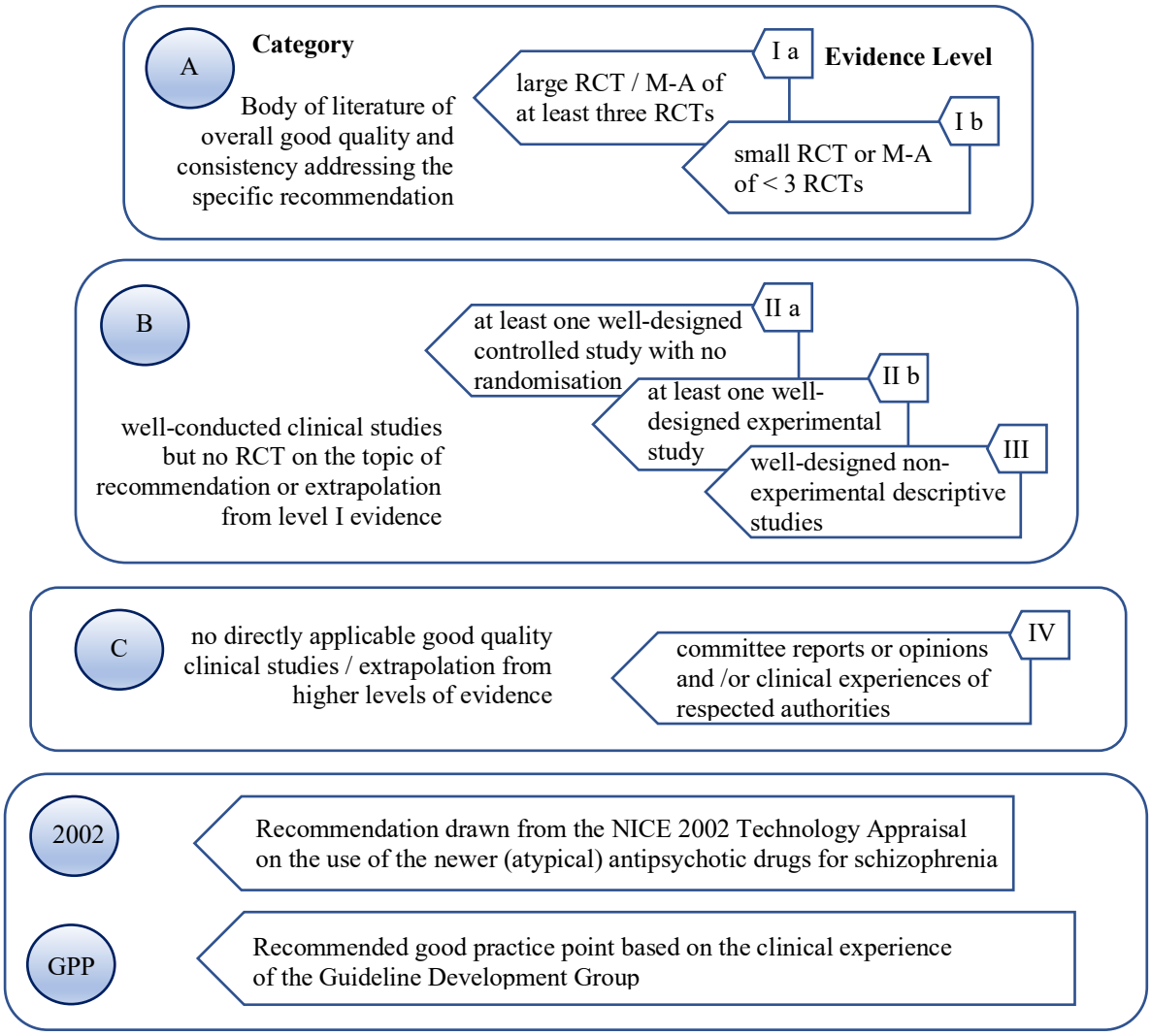
In hindsight, this description seems to combine the organisational mission statement with an explanation of the routine critical appraisal process - clarifying for the benefit of the intended users the aim to deliver a definitive guidance and conveying the reassurance that the process by which this guidance was synthesised is scientifically robust and impartial.

The evidence that formed the base of this guidance was obtained from existing published studies, graded for strength in accordance to the hierarchy of evidence (Eccles & Mason 2001) from level Ia ("large randomised trial or meta-analysis of at least three randomised controlled trials") to level IV ("opinions and/or clinical experiences of respected authorities") as illustrated appendix 1 of the Guideline. The recommendations were similarly graded from A to C, based on the strength of evidence that supported that specific recommendation - a model used before by the Clinical Outcomes Group of the NHS Executive (Figure 1). The Guideline put forward 69 recommendations and a further 40 Good Practice Points, out of which 44 were derived from the previously published NICE Technology Appraisal (43) (*NICE Technology Appraisal 43 - Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia*, 2002)

This high-quality evaluation was authored by a different group (other than the members of the Guideline Development Group) had a focus on the cost-effectiveness, and the recommendation derived from this work were given a distinct grading due to *"inevitable differences concerning ownership and style of recommendations* [which] *presented considerable problems of integration." (*Pilling & Price, 2006). Furthermore, some of the recommendations were based on the *"clinical experience of the GDG"* and were graded as "Good Practice Point"

Figure 1.

Grading of recommendations in Clinical Guideline 1based on the source of information and Hierarchy of evidence for studies reviewed in the development of Clinical Guideline 1



Note: Adapted from: *How to develop cost-conscious guidelines*, *Appendix A p.29 NICE CG1 (2002), based on* Eccles & Mason (2001) CC BY-NC and *ibid. Appendix A p.30* (based on a scheme from: NHS Executive. *Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care within the NHS.* London: 1996) CC BY-NC

One of the key recommendations in CG1, on the basis of evidence considered, was that oral atypical antipsychotics should be the first-line treatment for first episode schizophrenia – and that this was to be initiated in Primary Care if necessary.

Thus, the provision of paragraph 1.2 of the TA 43 advising *that "the oral atypical antipsychotic drugs amisulpride, olanzapine, quetiapine, risperidone and zotepine should be* ***considered in the choice of first-line treatments*** *..."* was modified in the CG1 by advice that *"atypical antipsychotics at the lower end of the standard dose* ***are the preferred treatments*** *for a person experiencing a first episode of schizophrenia"* (NICE, 2002)

There is a lack of transparent information on the exact studies included in the guideline development. By contrast, the TA 43 lists in appendix B the sources of evidence and makes clear that the main source was the "Rapid and Systematic Review of Atypical Antipsychotics in Schizophrenia" (2001) an assessment report prepared by the NHS Centre for Reviews and Dissemination, University of York, as well other sources, such as manufacturer/sponsor submissions by the pharmaceutical companies and other professional/specialist group and patient group input.

It is unclear how the guideline could have been developed without considering the summary of evidence presented in Geddes et al (2000) on behalf of the National Schizophrenia Guidelines Group (the joint initiative of the British Psychological Society and the Royal College of Psychiatrists). In this meta-analysis of 52 published randomised controlled trials including 12649 patients, the authors aimed to identify and quantify any pooled advantages of the atypical antipsychotics over the typicals and establish whether any clinically significant differences between individual drugs can be detected. The results indicated that some of the atypicals had a moderately better efficacy and a lower risk of extrapyramidal side-effects (Geddes et al., 2000) The caveat presented by the authors was that in the vast majority of the

studies included the comparator dose (haloperidol or chlorpromazine) was high. According to Bollini et al (1994) efficacy tends to plateau with the dose-increase, but the side-effects increase in a dose-related way (Bollini, Pampallona, Orza, Adams, & Chalmers, 1994). To counteract this effect Geddes et al. (2000) used meta-regression to control for the comparator drug dose, and by doing so the advantages of the atypicals reduced - both in terms of efficacy and tolerability (apart from extrapyramidal symptoms) – albeit this was later contradicted by a meta-analysis of existing evidence on the efficacy superiority of risperidone over haloperidol – which states that the effect cannot be justified by the dose of haloperidol used. (Davis & Chen, 2002; Davis, Chen, & Glick, 2003)

The conclusion would be that the new class of drugs, considerably more expensive than the old ones, are not more effective in reducing the psychotic symptoms and are not better tolerated save from a reduction in the extrapyramidal side-effects. Indeed, the concluding statement reads:

"Conventional antipsychotics should usually be used in the initial treatment of an episode of schizophrenia unless the patient has previously not responded to these drugs or has unacceptable extrapyramidal side effects" (Geddes et al., 2000)

It is difficult to ascertain how this high-level evidence has translated into the guideline.

Further critique brought to the guideline relates to its dependence on the existing systematic reviews, which may not address the exact clinical query that the guideline wants to answer. Pilling and Price (2006) acknowledges that *"time spent refining and revising often proved more time-consuming and less satisfactory than developing de novo reviews"* and give further consideration to the absence (or limited availability) of relevant research data in two areas:

a) pharmacological interventions in diverse age groups, like older or younger people (other than the generally termed ‘adults with schizophrenia’) as well as on clinical groups with significant comorbidities, such as learning difficulties or dual diagnoses.
b) long-term outcomes data on harm /hazard (such as diabetes and weight gain) due to the absence of long-term follow-up trials and the inaccessibility of unpublished data on from pharmacological trial results.

Although the authors recognise that this data is available from sources other than randomised clinical trials in databases of European drug regulatory authorities (the equivalent of the MHRA) as well as in the UK General Practice Research Database, utilising such sources would lead to an acceptance of further criticism that has been made to the methodological aspects of selecting and grading the evidence, as well as grading the recommendations based on the level of evidence at its origin. A proposal has been made by NICE in its consultation document “Making the Guideline Development Process More Efficient” that this system should be revised or abandoned. (NICE, 2005)

As a parenthesis it is worth noting that a number of editorials in the British Medical Journal around the time, highlight that whilst manufacturers have a legal obligation to provide the MHRA with all the information on the safety and efficacy of the drug for which a marketing authorisation is sought, the MHRA does not routinely share information provided by manufacturers during the licensing process. Also, NICE does not have statutory powers to demand information from manufacturers, and all it can do is to seek confirmation from the manufacturer on the “completeness of information” found in the public domain.

In recent years a trend has emerged in the systematic reviews towards a “horses for courses” approach rather than an insistence on a hierarchy of evidence with meta-analyses

and systematic reviews at the top and clinical consensus at the bottom. It is recognised that, whilst methodologically the most likely to eliminate (or account for) sources of bias, it may not be always the most appropriate to answer the research question. Proponents of this approach suggest that the grading of evidence should not be based solely on the methodological quality of the study but consideration should be given to whether the study type is adequate and sufficient for the type of question it aims to answer. (Petticrew & Roberts, 2003)

The National Collaborating Centre for Mental Health uses consensus methods when the published evidence is scarce for the specific clinical query, (for example on the pharmacological management of psychotic episodes in pregnant women (Pilling & Price 2006) and if the current evidence and recommendation grading system is kept in place would result in some well-established interventions being downgraded. This in turn has an impact on implementation at organisational level, as priority goes to implementing guidance and recommendations graded A or B and may send an unintended message to individual clinicians less versed in the intricacies of the methods in which NICE allocates a grade to the recommendations.

On the same point of methodological issues of studies included in the evidence base, it must be mentioned that a large number of the randomised controlled trials included are equivalence or non-inferiority trials as superiority trials are not sanctioned by the regulatory requirements. Healy et al (2007) believe that in such instance the guideline risks *"producing perverse effects"* by not *"[…] making clear that no treatment option currently come close to the kind of evidential threshold that would mandate their use in preference to other available agents"* (Healy et al., 2007) and in any case it is hard to translate *treatment effects* from RCTs into clinical practice *treatment efficacy* (Healy, 2001).

The majority of the studies used as evidence-base are placebo-controlled, however some of the outcome measure are surrogate (or proxy) measures. The validity of drop-out rates as "proxy measure of tolerability", and the lack of correlation with clinical measures of adverse effects (such as plasma prolactin concentration) has been queried (Roswell, 2001) for studies comparing quetiapine and chlorpromazine and quetiapine vs. haloperidol or placebo; the unreliability of measuring the side-effects is also highlighted by Taylor (2007), who points out that two of the most common side-effects (hyperprolactinaemia and tardive diskinaesia) will develop later than the standard six week of active trial treatment and as such are likely to be missed.

The main concern however revolves (in retrospect) around a host of issues relating to the sources of bias in the individual studies and of the body of evidence as a whole. In the last 5 years the research community has become increasingly aware of more subtle sources of bias, but arguably at the time of the guideline publication (perhaps naively) only the 'classic' conflict of interest by pharmaceutical industry (to select what data to present to regulators and which data to publish in support of product efficacy, safety and side-effect profile) has been on the radar.

A further criticism brought mainly by patient groups is that the type of outcome data available (used) in the guideline development focuses intently on symptom relief to the exclusion of other important factors such as quality of life and social functioning. This appears to be an issue of major importance, considering the impact the side-effect of antipsychotic medication on the quality of life and the fact that antipsychotics are a heterogeneous class of drugs and each drug has different benefits and side-effects and in turn these are of different importance to each patient.

The importance of choice is outlined in Prior et al. (2001) who highlight that data is available on patients' experience of treatments and not take it into account equates "*denial of choice"*

(Prior, Clements, & Rowett, 2001). This has been possibly put forward by the stakeholder group in the consultation for the revised guideline as studies on quality of life have been subsequently included in the evidence base.

Finally, at the time it was issued, the guideline received criticism for the way in which it was presented and disseminated, as a lengthy document with multiple appendices and was deemed to be in itself an obstacle to implementation. However, this is no longer relevant, as in recent years the paper versions of the NICE guidelines have become obsolete and replaced by a web-based application in which the full version of the guideline is supplemented by a quick reference guide and a patient version.

The evidence that challenged the guideline

"Over the last 10 years NCCMH has recognised imperfections and patterns of bias in the way that evidence is generated and included in the guidelines"

(Kendall, Glover, Taylor and Pilling, 2011)

The full follow-up guidance document issued in 2003 by the National Collaborating Centre for Mental Health and recommends that atypicals are to be "*considered in the choice of first-line treatments"* for people with newly-diagnosed schizophrenia (5.2.7.7) and not that they should be *the first-line choice*. Older atypicals and first generation drugs prescribed in "adequate but not excessive" dose (5.2.7.3) are also mentioned. (National Collaborating Centre for Mental Health (Great Britain), 2003)

This may well have been the first sign that the evidence base of the first NICE guideline was about to be challenged.

A HTA funded systematic review of atypical antipsychotic drugs in schizophrenia by Bagnall and colleagues (2003) looked at clinical effectiveness, safety and cost-effectiveness

of atypical antipsychotics in comparison with typical antipsychotic drugs or placebo. (Bagnall et al., 2003). An extensive data source updated the existing Cochrane reviews with randomised controlled trials of atypical antipsychotic drugs and observational prospective and retrospective cohort /case-control studies of long-term adverse events. The validity assessment criteria for included studies lists*: "adequacy of randomisation; adequacy of blinding; comparability of groups at baseline; attrition rate; adequacy of description of withdrawals; adequacy of intention-to- treat data analysis; appropriate dose of comparator drug; adequate washout period"*, and for non-randomised studies adherence to the NHS Centre for Reviews and Dissemination (CRD) criteria was quoted. Over 170 effectiveness studies and a further 52 safety studies were included, including some *35 "wholly or partly commercial-in-confidence data from drug manufacturers"*.

The first assessment of validity the authors make brings into discussion the strength of evidence of studies that were the initial evidence base for the NICE guideline, and label it *"poor quality"* […]*" based on short-term trials"* and […] *"difficult to generalise to the whole population with schizophrenia".* Furthermore, the authors highlight that this is not only applicable to comparison between first and second generation antipsychotics, but also to the strength of evidence comparing effectiveness between various second generation antipsychotics and state unequivocally that *"the conclusions are based on limited evidence and should be treated with caution"* (Bagnall et al., 2003).

The review concludes that on the basis of available evidence some atypicals (olanzapine, risperidone, clozapine and amisulpride) were *"more effective than typical comparators"* in controlling psychotic episodes, whilst others (quetiapine and sertindole) had no demonstrable superior efficacy. Using attrition rate as a surrogate measure for tolerability/acceptability the authors conclude that there is evidence atypicals were found more acceptable.

When looking at side effects, atypicals were found to cause fewer movement disorders but more autonomic side-effects (with the exception of olanzapine), and demonstrably increased weight-gain and cardiotoxicity. However, the authors are keen to highlight that as far as side effects are concerned *"issues such as dose or definition and reporting of symptoms limited the confidence that can be placed in these results"* (Bagnall et al., 2003).

This systematic review was supported by a subsequent Cochrane Review which looked at the results of randomised controlled trials of efficacy and safety of typicals versus atypicals (amisulpride, risperidone, olanzapine, quetiapine, clozapine and zotepine) in first episode schizophrenia and concluded that there is not enough evidence in the published RCTs to establish whether the use of atypicals makes treatment *"less off putting and enhances long-term compliance"* (Johannes Hamann et al., 2003). The authors mention however, that when assessing the quality of the studies to be included in the review they excluded studies with more than 50% loss to follow-up, which arguably defeats the object of a review looking at tolerability of treatment and introduces a bias by excluding negative results.

A plethora of systematic reviews of individual atypicals versus typicals, placebo and other atypicals were conducted between 2002 and 2009 and all lead to the same conclusion.

Amisulpride was deemed to be more effective in improving global state, general mental state and negative symptoms of schizophrenia and "as effective" as typicals, less likely to cause general adverse events and extrapyramidal symptoms, but no clear differences in other adverse events could be established. It is also deemed to be "more acceptable" than typicals by using study drop-out rate as proxy outcome measure - but the authors acknowledge that a publication bias might have lead to this being overestimated. (Silveira da Mota Neto, Soares, & Silva de Lima, 2002)

Risperidone was deemed to show *"limited"* clinical benefits but more 'acceptability' than typicals. The authors are keen to point out that *"Any marginal benefits this drug may*

have to be balanced against its greater cost and increased tendency to cause side effects such as weight gain." (Hunter, Kennedy, Song, Gadon, & Irving, 2003)

A review of studies comparing quetiapine to typicals and placebo has shown it to be *"not much different"* in efficacy and tolerability (by proxy measure), lower incidence of movement disorders but higher risks of autonomic side-effects. (Srisurapanont, Maneeton, Maneeton, Lankappa, & Gandhi, 2004)

Zotepine was shown (DeSilva et al., 2006) to fare better than placebo and "*as effective*" as typicals on mental state ratings, but with the same tolerability: one third attrition rate before trial completion in both the intervention and controls groups. (DeSilva, Fenton, & Rathbone, 2006)

A review of studies comparing aripiprazole with typicals, other atypical antipsychotics and placebo, concluded that RCTs show its effectiveness in the treatment of schizophrenia - but not a great difference in *"treatment response, efficacy or tolerability", and* is *"comparable* [to typicals] *in improving global state and mental state".* It "*may have"* lower risk of extrapyramidal symptoms, a reduced risk of akathisia, and in comparison to other atypicals a lower risk of hyperprolactinaemia and cardiotoxicity[4] (El-Sayeh & Morganti, 2006) – which is interpreted as the possible cause for a lesser attrition in the aripiprazole groups over comparators (Bhattacharjee & El-Sayeh, 2008).

Finally, the review of clozapine versus typicals shows a higher rate of effectiveness in "clinical improvements" (possibly in BPRS scores symptom reduction) and fewer relapses in the clozapine groups. Clozapine was also found to be more acceptable (despite increased

[4] This was only partially supported by a later Cochrane Review (Khanna et al., 2014) which included 174 studies with a total of 17,244 participants comparing aripiprazole with clozapine, olanzapine, risperidone, quetiapine and ziprasidone – which found no significant differences between groups for global state, mental state or drop-out rate; authors note that the absence of longitudinal follow-up data and the low quality of evidence makes it problematic to use clinically.

occurrence of autonomic side-effects but possibly due to lesser motor disturbances) but trials have not shown an improvement in measures of global functioning. (Essali, Al-Haj Haasan, Li, & Rathbone, 2009). All Cochrane Reviews acknowledge the limitations of the studies included and call for more research to objectively assess global and social functioning and elicit the views of patients and carers on acceptability and tolerability.

The reviews were followed by two large-scale high quality randomised controlled trials. The first one looked at the comparative effectiveness of a typical (perphenazine) and four atypicals (olanzapine, quetiapine, risperidone and ziprasidone) in patients with chronic schizophrenia: "Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)". Albeit not directly related to the first-line intervention, the trial delineated the efficacy of each treatment reflecting variations in efficacy (reductions in positive and negative symptoms) and tolerability (i.e. therapeutic benefits vs. side-effects). The primary outcome measure was discontinuation of treatment and secondary outcome measures were the reasons of and time to discontinuation as indicators of efficacy and (in)tolerability due to prevalence of side-effects such as extrapyramidal side-effects and weight gain. The trial demonstrated that olanzapine alone was more effective than perphenazine in terms of rates of discontinuation and time to discontinuation but was associated with greater weight gain and metabolic side-effects. Efficacy of quetiapine, risperidone and ziprasidone was no different from perphenazine. (Lieberman et al., 2005)

The second trial looked at comparative efficacy and quality of life in typical and atypical antipsychotics "First generation versus second generation (non-clozapine) antipsychotic drugs versus clozapine in schizophrenia: The CUtLASS trials" - its main outcome measure patients requiring change of medication due to inadequate response or to address adverse effects. The trial blind-assessed QoL scores, prevalence of symptoms, adverse effects at 12, 26 and 56 weeks, as well as conducting an economic evaluation and a

patient satisfaction / quality of life measure in 227 participants. It results suggested that the atypical antipsychotics did not make a significant difference in symptoms or Quality of Life measures when compared to typicals, on the contrary, patients randomised to typicals *"showed a trend of greater improvement in QoL and symptom scores"* (Jones et al., 2006) and *"reported no clear preference for either drug group"* (Lewis et al., 2005)

Both studies above have similar conclusions, but critiques brought to the CUtLAS study highlight potential recruitment /selection bias towards patients with a certain characteristics, such as non-compliance: as the randomisation provided only the treatment group whilst the selection of specific formulation was chosen by the clinician it is possible that clinicians were reluctant to refer patient in which the benefits of a typical depot formulation (to avoid non-compliance) would outweigh the potential benefits of atypicals. Constantine (2007) also cites possible bias introduced by the clinicians as a significant percentage of patients who entered the trial as treatment-resistant were then allocated to an atypical (88%) vs 70% assigned to a typical.. Furthermore, the transferability of the findings in relation to extrapyramidal side-effects from chronic patients to first-line intervention is limited: patients in the trial had a low baseline measure of extrapyramidal side-effects as the mean duration of illness (and therefore treatment) was 14 years. (Constantine & Tandon, 2007)

A large meta-analysis of atypical versus typical antipsychotic medication for schizophrenia was conducted by Leucht et al. (2009) and produced the definitive summary of evidence on comparative efficacy, positive and negative symptom reduction, relapse, quality of life outcomes and side-effects. The study included 150 double blind randomised controlled trials (including CATIE and CUtLAS) with over 21,000 participants and excluded open label studies. The meta-analysis demonstrates that amisulpride, clozapine, olanzapine and risperidone have (a small to medium effect size) increased efficacy over typical antipsychotics, but this effect could not be demonstrated for the other atypicals. Atypicals induced fewer

extrapyramidal side-effects than haloperidol but this effect is not sustained when compared to low-potency typicals. The reverse effect has been shown for weight-gain: all atypical antipsychotics with the exception of aripiprazole induced more weight gain than haloperidol but not than low-potency typicals. (Leucht, Arbter, Engel, Kissling, & Davis, 2009)

Updated and revised guidelines

"The short answer is that there is not much of a difference"

"[…] *patients could at least choose between being stiff and putting on weight"*

(Kendall, 2011)

The NICE Clinical Guideline 1 was revised in 2009 based on the evidence published in the interim, and an updated guideline was issued: *"NICE Clinical Guideline 82: Schizophrenia Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care: an update of NICE clinical guideline 1"*

The accent on use of atypicals as first line intervention was removed, the recommendation for pharmacological intervention is to *"offer oral antipsychotic medication"* and specified that *"The choice of drug should be made by the service user and healthcare professional together, considering: the relative potential of individual antipsychotic drugs to cause extrapyramidal side effects (including akathisia), metabolic side effects (including weight gain) and other side effects (including unpleasant subjective experiences); and the views of the carer if the service user agrees."* (1.2.4.1) (National Collaborating Centre for Mental Health (Great Britain) et al., 2010)

This content of the NICE guidance and the conclusions of the studies that contributed to its revision is reflected in the 2010 updated edition of the NCCMH guidance: the myth of

superiority of the atypicals was dispelled by a clearer view that there is no significant clinical effectiveness or cost-effectiveness difference between typical and atypical antipsychotics, and that the various side-effects were not directly attributable to a specific class of drug; it also provided support for the clinician to identify the agent that benefits most an individual patient: as efficacy profiles seem to be similar, the choice of antipsychotic should be based on the relative tolerability of the prevalent side-effect.

Poignantly, in a 'posthumous' commentary on the utility of Clinical Guideline 1, one of its authors acknowledges a *"collective misunderstanding"* about atypicals, and recognises that *"the differences* […] *in terms of potency, efficacy and side-effects* […] *have been overplayed and systematically linked to a class effect"* (Kendall, 2011)

The updated guideline did not seem to curtail the interest in further research on the topic of antipsychotics, perhaps as almost all reviews highlighted the limited generalisability and the poor quality of existing studies. However, the focus seems to now have shifted from safety and efficacy of individual atypicals to identifying side-effects, looking at general and cognitive functioning, patient satisfaction and engagement, service outcomes and economic evaluations.

A meta-analysis by Crossley et al (2010) looked at data regarding discontinuation rates (at 12 months), efficacy (scores of symptom changes at 12 weeks), extrapyramidal and metabolic side-effects of 15 RCTs comparing typical (haloperidol, chlorpromazine, zuclopenthixol and sulpiride) and atypical (risperidone, olanzapine quetiapine and clozapine) antipsychotics in the treatment of early phase psychosis. The added value of this meta-analysis is that its results come from trials comparing low dose typicals (below the 12mg Haloperidol cut-of point) and thus eliminates the confounder of quantifiable higher side-effects resulting from a dose non-equivalency. The authors conclude that, whilst there is

difference in efficacy, there is a statistically significant (and clinically relevant) difference in the side-effect, with typicals being responsible for a higher rate of extra pyramidal side-effects (SMD -0.1 (95%CI -0.2 to 0.02)) and atypicals for a higher weight gain (mean 2.1kg (95%CI 0.1 to 4.1)). (Crossley, Constante, McGuire, & Power, 2010). The limitations of the analysis may come from the definition that various trials gave to 'discontinuation' and the pooling of the reasons thereof (lack of treatment response or intolerability of side-effects) – which means a higher heterogeneity of studies. Similarly, the efficacy was measured by symptomatic remission - but the scales were heterogeneous (some studies reported PANSS scores, some BPRS scores), and extra pyramidal side-effects may have been confounded by pooling the results of studies using high-potency haloperidol with studies randomising to chlorpromazine - and the use of several scales (SAS, ESRS, SHRS, etc) some measuring dystonia and akathisia, some parkinsonism and some the subjective experience of symptoms. However, the pooled results of all studies show a large effect size in the comparison of symptom scales but with the confidence interval crossing the line of no significance.

A systematic review undertaken by Belgamwar and colleagues, (2011) looks at nine randomised controlled trials comparing aripiprazole vs. placebo in 2585 patients and draws conclusions that may renew the debate on the validity of short-term intervention data: aripiprazole demonstrably decreased relapse in short and medium term and its safety profile shows a lower risk of hyperprolactinaemia and prolongation of the QT interval, but had very high attrition rates in studies lasting longer than 4 weeks.. Authors were unable to identify any of the patient satisfaction and service outcomes and conclude that more research is required to its relevance for clinical practice, (Belgamwar & El-Sayeh, 2011) thus giving a clear indication that findings related to safety and efficacy are no longer sufficient to inform the clinical decision making process.

Attempts to answer the long-term outcome questions are confounded by the nature of the management of a chronic condition. A paper by Girgis et al (2011) looking at long-term outcomes (remission status, attrition/change of medication, occurrence of extrapyramidal and metabolic side-effects) of patients who took part in an earlier RCT of clozapine versus chlorpromazine reports no difference between groups in remission or relapse, no difference in the metabolic side-effects and a statistically non-significant trend of higher incidence of tardive dyskinaesia in the chlorpromazine group. Albeit all findings are consistent with the profiles of the two drugs – and the findings of the initial trial which showed no difference at 52 weeks in the efficacy profile - the authors acknowledge the limitations resulting from the observational "naturalistic" design of the study, and the fact that in the nine year since the end of the initial trial the majority of participants would have taken a number of other drugs and therefore a potential for crossover between groups exists. (Girgis et al., 2011)

This paper in fact highlights the quintessential problem of designing and conducting long term trials with minimal bias and where all confounding factors can be identified and factored in the analysis: schizophrenia patients are by definition contenders for polypharmacy and/or a change in the class of drug as efficacy diminishes or side-effects become bothersome.

This may be the reason why very few long-term studies exist and monitoring of side-effects has been largely left to routine clinical practice rather than research papers. Existing systematic reviews and meta-analyses face the methodological challenge of heterogeneity of included RTCs, with different outcome measures and follow-up periods for selective side-effects, as well as lack of information from unpublished data. Therefore, published reports do not have the 'evidence weight' required to alter the perception of the safety profile of individual drugs.

The evidence used by the MHRA to licence and regulate the use of a drug is reportedly different from the evidence used by NICE when formulating its guidelines and

recommendations. Whilst the MHRA licenses a drug based on submitted safety and efficacy data of the manufacturer, NICE uses published comparative trials of an intervention versus treatment as usual (TAU) or placebo and ranks findings/ recommendations based on the methodological strength of the trials included in the review. In its monitoring practices the MHRA (and as a matter of fact the European Medicines Agency) insists on post-marketing phase IV observational registries /surveillance studies – which are seldom available or constitute methodologically 'weighty' information for a NICE review.

Furthermore, the information available from Pharmacovigilance Working Party Public Assessment Reports are outdated (the cardiac safety report was issued May 2006 with a data a lock point August 2001; the cerebrovascular events report was issued in 2005, the increased mortality report was issues 2008, and the thromboembolic events report in 2009) and confusingly reports the sources of evidence as: *"experimental data, clinical trials, literature reviews, case histories, spontaneous reporting, meta-analyses and epidemiology for each drug substance. Marketing authorisation holders for each drug were also asked to provide an assessment of risk of cardiotoxicity for their products* […]" (MHRA, 2005, 2009)

In an article reviewing the impact of 10 years of guidelines in Mental Health, Kendall et al. (2011) highlight the fact this inconsistency is compounded by the fact that not all data is published by the manufacturer and there is very little transparency on how the MHRA considered the unpublished data; moreover, prescribers have no access to this data at all (Kendall et al., 2011), but are in receipt of MHRA warnings issued over a specific drug or class - at the same time as being subjected to the "highly effective marketing strategies" by the manufacturers. Methodological issues identified by the authors highlight findings that bias in trials is wide-spread – citing findings of reports of trials comparing a drug with placebo are more likely to *"report favourable results for the drug produced by the company*

funding the trial" (Lexchin, Bero, Djulbegovic, & Clark, 2003) and trials comparing drug vs. TAU *"almost invariably find in favour of the company funding the trial"* (Heres et al., 2006) It is not the object to this paper to discuss in detail the methodological issues raised by 'marketing trials' as they are well-known and acknowledged by the scientific community. Barbour and colleagues (2016) identify details indicative of marketing *'features'* such as attributional spin, and framing the research question, choosing the study design and a reporting strategy to serve a marketing goal – and conclude that their analysis found these features in 1/5 of trials published in the high-impact journals in 2011 (Barbour et al., 2016) It is however noteworthy that these characteristics are not easily identifiable by clinicians (Matheson, 2017) and do not appear to have been taken into consideration by the guideline development group, or at least this criteria does not appear explicitly in the selection and hierarchy description, beyond the usual 'declarations of interests'.

A third evaluation of the text of the guideline in relation to existing evidence lead to its reformation in 2014: CG 82 is *replaced* by "CG 178: Psychosis and schizophrenia in adults: prevention and management" (NICE, 2014). The first thing to note is that the guideline now no longer refers to schizoprenia alone but incorporates psychosis. As 'psychosis' is not described as a distinct disorder by either ICD or DSM its diagnosis is very much based on individual experience and local service guideline and threofere subject to variability. The guideline aims to address this by defining psychosis and schizophrenia as an umbrella term for cluster of major psychiatirc disorders disorders to include schizopreniform disorder, schizoaffectie disorder and delusional disorder – presumabley to cover the shift between DSM-IV and the (then) recently introduced DSM-5.

The novel approach is person-centred care and the recognition that schizophrenia will not be identical in all patients and the pattern and duration of symptoms patients will exhibit will

vary considerably between individual patients. This has both positive and negative implications. In the first instance it is a step in the right direction as it encourages tailored care and individualised treatment, but it adds a ‘nail to the coffin’ of differentiating between psychiatric and somatic conditions, and schizophrenia is now licenced to find itself on a spectrum of symptoms that may mean that the label itself becomes meaningless. In fact, on the advent of the guideline, the Schizophrenia Commission recommended caution in using this diagnosis during early intervention as it generates stigma and is unhelpful to treatment (Schizoprenia Commission, 2012)

The other important addition is a very specific indication for psychological interventions: whilst in CG82 psychological and psychosocial interventions are listed as a possible option, in CG178 they appear in a distinct section with very precise indications and directions. In fact, only about 20% of the recommendations now refer to pharmacological interventions and most of them refer to a combination of pharmacological and psychological interventions (Perera & Taylor, 2014), but the guideline developers argue that there was insufficient new evidence since the publication of the CG82 to warrant a review of the evidence for pharmacological interventions and they focused instead on expanding areas that did have new evidence, such as early intervention, assertive community treatment, self-management and carer experience.(Kendall et al., 2016).

It is worth noting that, just as with pharmacological interventions mandated by CG 1 for which the evidence lacked information on side-effects and adverse effects from long term studies to support the recommendation of prescribing atypical antipsychotics, CG178 lacks evidence to inform on potential side-effects of psychological interventions (such as deterioration due to overstimulation or added burden due to poorly quality assured interventions or patchy resource). A contemporaneous meta-analysis concludes that CBT has a small therapeutic effect on both positive and negative symptoms and this effect further

diminishes when sources of bias, such as masking or outcome assessments and incomplete data on outcomes or control interventions are accounted for. (Jauhar et al., 2014)

The recommendations on choice of antipsychotic medication are somewhat vague, but the guideline introduces detailed direction on physical health assessment at baseline and subsequent monitoring for unwanted changes signalling iatrogenic harm. It does not make recommendations based on more recent evidence from a meta-analysis which clarifies modest efficacy differences between antipsychotics and virtually produces an evidence-based hierarchy of efficacy and tolerability and side-effects (Leucht et al., 2013), nor does it mention dosing differences between first episode and maintenance – perhaps relying on BNF guidance. The recommendations reflect the ethos of this iteration of the guidance that treatment is individualised, a choice made by clinician and patient in collaboration.

Faced with this challenge, the questions that airse are: “What helps clinicians decide what drug to prescribe?”, “How much and what type of information do they need/want/can process to make the decision on the optimal therapeutic intervention for the individual patient?” and, in the context of practicing Evidence Based Medicine, “What counts as evidence and how is this evidence interpreted and what other factors contribute to the decision-making process?”

Practicing Evidence-Based Medicine - synthesis of trends

> *"new evidence […] invalidates previously accepted diagnostic tests and treatments and replaces them with new ones, that are more powerful, more accurate more efficacious and safer"* (Sackett, Strauss, Richardson, Rosenberg and Hayes, 2000)

The purpose of this chapter is to outline and describe the advances in Evidence-Based Medicine as a concept, a dimension of knowledge translation and a working practice - and to map out the barriers to implementation and knowledge translation resulting from the contextual developments in 'evidence'. It aims to highlight what we know about the difficulties with 'evidence' that may influence the way in which this is translated and implemented into clinical practice. Factors intrinsic to the 'research evidence' as well as extrinsic (the way in which the evidence synthesis is constructed into guidelines) are discussed.

The chapter demonstrates an acknowledgment in the clinical community that published studies have flaws and/ or are deemed incompatible with clinical practice, and that universal models of care are (most of the time) not applicable to particular clinical scenarios. Extrinsic factors discussed include a discussion of guideline developments, by which different guidance developing forums (NCCMH, NICE, Cochrane Collaboration) look at different bodies of evidence, and the value of the studies and strength of evidence are graded on different grading scales.

Furthermore, the value of evidence is different to different stakeholders: if evidence has to integrate patient values and clinical experience, then the knowledge derived from clinical experience has evidence value. Qualitative studies must have a higher categorisation, to count as as evidence value.

This chapter makes the point that not the choice of methodology but the quality of design and conduct of the study should determine the strength of evidence; dynamic quality and clinical expertise has to integrate research evidence and patient factors.

The crux of the concept of Evidence-Based Medicine (EBM) rests in the acknowledgement that the 'book of medicine' is not closed and science is knowledge in progress; we make observations and 'guess' an explanation of that observation; we then can make a prediction that we can test with an experiment or other observations. As a concept EBM has undergone several transformations from its initial coining, but it remains anchored in the need to base clinical decisions on the best possible scientific evidence.

The journey from Eminence-based medicine to Evidence-Based Medicine was a natural evolution of scientific curiosity and largely fuelled by the social transformations at the beginning of the 20th century.

Up until the end of the 19th century, learning the art and science of medicine in general, and its practical application as "clinical decision-making" in particular, was a very different affair from what we know today. In a model of "eminence-based" medicine, grand masters of the profession imparted knowledge, habitually pontificating on ward rounds, followed by fresh-faced residents in floppy white coasts eager to learn from the maestro's encyclopaedic knowledge. The background knowledge came of course from lectures and practical demonstrations in amphitheatres of the grand European universities, and from the medical textbooks - but to round up a career a newcomer to the profession was invariably expected to shadow for a good few years a senior figure-head of the establishment.

This was the model 'de rigueur' and the only way to build a career; the more famous the maestro and the institution, the better the chances of landing a good position and a future solid clientele. Being labelled a 'student of X' was the equivalent of a fast-track career, if

Professor X was himself the head of school. A recommendation from an eminent Professor X was sufficient to decide the outcome of any exam.

As a method, it had numerous advantages (seen in historical perspective) - in that the mentorship that was given to gifted and acquisitive students formed a very solid knowledge base and it often resulted in honing some of our most successful thinkers, medical practice reformers and great contributions to the advancement of medical science.

Some 'grand masters' practiced this model with more gusto than others. For example, Charcot's propensity for a self-assured arrogance stemmed probably from his comprehensive knowledge (he was himself an eminent student of Duchenne) and it is said that one aquiline look at the patient was all it took for him to pronounce a firm diagnostic (Harris, 2005) and that the patient presented no further interest to him from that moment on (Munthe, 1929). He worked tirelessly and demanded the same from his 'assistants' many of whom developed an appetite for research and went on to publish seminal works in neurology and psychiatry.

Its drawback though was that this close bond shaped disciples in the same mould as their maestro and channelled their creativity in a style of the 'school of thought', to the detriment of open-mindedness, "*we see only what we are ready to see, what we have been taught to see* […] *we eliminate and ignore everything that it's not part of our prejudices"* (Kundu, 2004) – unless of course the open-mindedness and keenness for research was part of the 'school of thought'. In hindsight, possibly the greatest drawback of the method was that the knowledge passed on was based on limited or evolving evidence and that research often was observational or small-scale interventional case series, with an inherent risk of bias. It has however the great merit that it introduced a need for results of research to be incorporated into the practice of medicine and epitomised the value of scientific curiosity.

It's equally true that this was the preserve of the elite: the vast majority of medical students did not go on to be mentored by an accomplished Professor and based their practice

on knowledge they accumulated in school, and supplemented it haphazardly throughout their career with attendance of learned societies or reading medical journals - if pushed by curiosity. This left individual clinicians to determine their own way of making a 'clinical judgement' and decide for themselves what new knowledge to incorporate (if any) in the treatment of their patients.

By the beginning of the 20th century we see a thought revolution in the quest for the application of a scientific method to the way in which 'clinical judgment' should be built. This was largely based on the recognition that clinical judgement tended to be highly subjective, based largely on their own clinical experience and - if it incorporated new scientific discoveries - it has no means of *assessing* the value of the 'new addition'.

Probably a consolidated effort in reforming clinical decision-making started with Feinstein's book in 1967 highlighting just how much individual bias affects clinical reasoning, and postulating that individual clinician distrustful of 'new science' should apply Boolean algebra to the study of clinical populations if any inference drawn is to help facilitate clinical management. (Feinstein, 1967). This was followed by another seminal work in 1973 by Wennberg and Gittelsohn's documenting the large variation in clinical practice resulting from individual subjectivism and noting the need for population-based health information to guide care-planning and regulate decision-making.

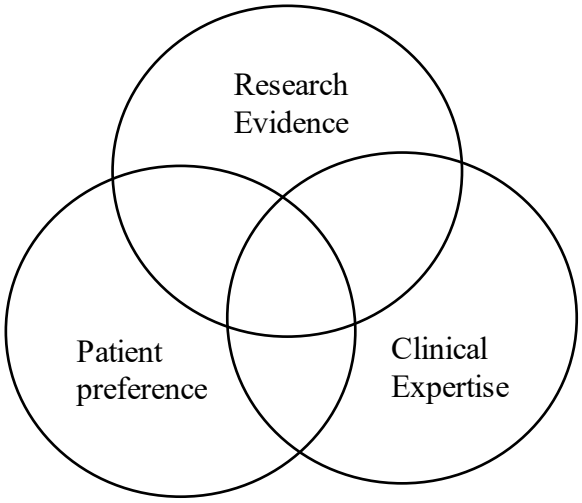
To add depth to our understanding of individual sources of bias, Sacket and Altman developed a series of works highlighting that a very large proportion of procedures and therapeutic interventions either lack of scientific evidence or the evidences lacks 'robustness' – on the foundation of Cochrane's earlier work (1972) on *Effectiveness and Efficiency*, which set in motion the modern epidemiological approach by advocating the use of bias

reducing methods (such as randomized control trials) to generate the evidence to support and effective clinical practice.

This was the birth of 'evidence-based medicine' as a concept which will replace and make obsolete the eminence-based medicine from whence it stemmed. It advocates integrating (Figure 2) the *"best possible evidence"* with individual clinical expertise and considering patient values in the mix (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). The notion of "best" (in terms of research evidence) is confined to *critically appraised "rigorous clinical research"* and this generated a rigid hierarchical allocation of significance and value to studies that may contribute information to aid decision-making.

Figure 2.

Diagram of Evidence-Based Medicine based on Sackett and Rosenberg's initial model



Source: based on Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: what it is and what it isn't. *BMJ (Clinical research ed.)*, *312*(7023), 71-2.

The authors advocate that the practice of EBM is a circular process and self-directed learning plays an essential part. Clinicians are to define clinically relevant information needs, identify and critically appraise the evidence, apply the results and evaluate their outcome. If this process is generalised, EBM becomes a common language by which the 'rules of evidence' are communicated.

What counts as evidence and how is strength of evidence measured

"Not all that is measured is of value

and not all that is of value can be measured." (Bradley, 1991)

Although the working definition and categories have been developed and refined since its inception, the principle of EBM remains the same: the clinical question determines the nature and source of evidence to be sought; it is a cyclical, continuous, process (Guyatt, Cairns, Churchill, & al, 1992), and all clinical interventions should be validated by controlled trials (Sackett, Ellis, Mulligan, & Rowe, 1995), with the value of that evidence weighed by methodological considerations.

The University of Oxford Centre for Evidence Based Medicine has defined 'Levels of Evidence' based on the critical evaluation (following a CASP model) of the design and conduct of the study - for all therapy/prevention, aetiology/harm, prognosis, diagnosis prevalence studies and economic analyses. (table 4). This was developed in 2009 based on earlier work by Sackett, Straus, Haynes, and Dawes (1998) and is supplemented with a very specific grading of recommendations that can be made based on the value of evidence, where a grade A is supported consistently by level 1 studies, B by level 2 or 3, C by level 4, and D by level 5 evidence or inconclusive /inconsistent evidence at levels above, such as wide confidence intervals or large heterogeneity of studies included in the review.

The prescriptive specifications for 'level of evidence', accompanied by the normative design and conduct assessments resulting from the critical appraisal are paramount in determining the strength of findings of a particular research. As a result, the strength of recommendations made by NICE is a direct product of the level of evidence (table 4), therefore only a particular type of evidence will result in a recommendation of A grade.

It is important to note that the strength of evidence has an impact on its translation in clinical practice. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) group - who worked to develop a standard of grading the quality of evidence and the strength of recommendations in guideline development - note that in practice clinical decisions may differ based on individual clinician's interpretation of whether the study is *'convincing'* or *'unconvincing'*. Correspondingly, the strength of the recommendation in a guideline identifies whether *"all patients definitely should be treated or that patients should probably be treated, implying that treatment may not be warranted in all patients"* (Guyatt et al., 2009)

It is interesting to note that in keeping with the cyclical nature of evidence appraisal, GRADE has employed a similar review technique to their grading criteria: the initial version was issued in 2008, was later edited by Oxman and Guyatt (2009), reviewed by the working group as a whole in 2010 and updated in 2016, and the group maintains a live database of evidence profiles and recommendations. Since the beginning of the Critical Appraisal programmes various organisations employed various systems to assess the quality /level of evidence and to grade the recommendations. *"The same evidence and recommendation could be graded as "II-2, B", "C+, 1", or "strong evidence, strongly recommended" depending on which system is used […] For treatments this will generally mean consistent results from high quality randomised trials or a systematic review. Guideline recommendations alone are usually insufficient: they may be based on weak evidence or may not have been developed using an evidence based process"* (Glasziou et al., 2012)

Whilst NICE has developed and uses the system described above, the Cochrane review authors now use the GRADE system. Albeit there is not a striking difference in the two grading systems, discrepancies can occur in allocating *levels of evidence* to the assessed material, which will in turn result in a different *grade of recommendation*.

Moreover, there is a discrepancy between the type/level of evidence and trial design requested by the regulatory authorities (EMEA in the EU, the MHRA in the UK) and the design required to "make the mark" of OCEBM (used universally to assess the quality of evidence). Currently, in their endeavour to comply with methodological rigorous standards, trial data submitted for marketing authorisation to the licensing authority is very often resulting from either placebo-controlled trials or non-inferiority trials. (Cambridge Econometrics , CES IFO, 2009). This has resulted over the years in a number of 'me too' products, offering similar outcome or marginal therapeutic improvement, and prescribers do not have the information on the *comparative* clinical efficacy or safety profile (Naci, Cylus, Vandoros, Sato, & Perampaladas, 2012)

There is a pressure to incorporate data on their equivalence and comparative efficacy (non-inferiority or superiority) to existing alternatives (Goldberg, 2011; Sorenson, Naci, Cylus, & Mossialos, 2011; Stafford, Wagner, & Lavori, 2009) or demonstrating 'added value' (Barbui & Bighelli, 2013) and regulators also stated (in EMEA's case) that it would favour data from *"three arm non-inferiority trials including the experimental drug, placebo, and active control - when the use of placebo is deemed ethical and one or more established medicines are available"* (EMEA, 2010) and would offer an extended marketing protection period up to 11 years for products with demonstrable improved efficacy or safety over existing treatments. Expectedly, the pharmaceutical industry resists the requirements for data that would result in increased costs and duration in clinical trials aimed to demonstrate superiority with possibly multiple comparators (Paul et al., 2010)

However, there is no clarity regarding the level of evidence standard required to obtain the marketing authorisation and therefore it cannot be ascertained whether data from the authorisation trials would pass the mark set by OCEBM and used by the National Collaborating Centres to assess evidence for NICE. This issue is compounded by the fact that efficacy is

often established based on surrogate outcome measures in authorisation trials, not on clinical endpoints. Even in the case of the comparative trial proposed by EMEA a coherent picture of efficacy will not be known until the drug has been in circulation for a number of years; This is acknowledged by licensing authorities who now request as standard the post-marketing surveillance registry/study – but such studies will not reach the "level of evidence" value required to make the appraisal shortlist.

This discrepancy and need to synchronise requirements between the requirements of regulatory authorities and of health technology assessors , such has NICE, Cochrane Collaboration, NIHR, NCCMH, etc (Alexander, O'Connor, & Stafford, 2011) somewhat compromises the concept of 'evidence' in EBM. Even if a solution could be found to this issue, a further factor with major impact on translation of research findings in clinical practice is the fact that methodological rigour of the trial seems to be perceived differently based on the source of funding. A recent study by Kesselheim, Robertson Myers et al (2012) has investigated the effect of clinical trial funding on interpretation of trial results and willingness to prescribe. The team presented a sample of 503 clinicians (269 respondents) with the abstracts of trials of hypothetical drugs, with high, medium or low methodological rigour and one of three possible 'support' disclosures: pharmaceutical company funding, governmental funding (NIH) or none mentioned. Whilst the majority of respondents accurately identified the true rigour of the study, a disclosure of industry funding led clinicians to arbitrarily downgrade the level of methodological rigour of a trial. The willingness to prescribe was also influenced by the study sponsorship: clinicians were half as willing to prescribe drugs studied in industry funded trials then NIH funded trials.(Kesselheim et al., 2012)

The authors attribute the ‘scepticism’ and negative association between the trial rigour and funding source to the mediatisation of *“occasional scientific and ethical lapses in trials funded by pharmaceutical companies”* and highlight that this in fact hinders the appropriate translation of knowledge as the prescribing decision is often made on the basis of a single published study.

The fact that clinicians do not trust industry sponsored studies is not new: the New England Journal of Medicine published in 2008 the result of a poll of its readers’ opinions on whether the results of a published trial (JUPITER: Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) would justify a change in the clinical practice. The majority of the respondents *“expressed concern about the effect of the pharmaceutical industry on the results”* and raised a number of methodological issues to justify their opinion that this trial is not adequate evidence to change practice.(Kritek & Campion, 2008)

Table 4.

Levels of Evidence and strength grades of recommendations (Oxford Centre for Evidence-based Medicine)

Grade	Level	Therapy	Prognosis	Economic and decision analyses
A	1a	SR (with homogeneity) of RCTs	SR (with homogeneity) of inception cohort studies; CDR algorithm validated in different populations	SR (with homogeneity) of Level 1 economic studies
	1b	Individual RCT (with narrow CI)	Individual inception cohort study with > 80% follow-up; CDR validated in a single population	Analysis of clinically sensible costs /alternatives; SR of evidence / multi-way sensitivity analyses
	1c	All or none (all patients died before the Rx available, but some now survive on it/ some patients died before the Rx available, but none now die on it)	All or none case-series	Absolute better-value (as good but cheaper / better at the same or reduced cost) or worse-value (as good but more expensive / worse but equally expensive)
B	2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of retrospective cohort studies /untreated control groups in RCTs	SR (with homogeneity) of Level >2 economic studies
	2b	Individual cohort study/low quality RCT (<80% follow-up)	Retrospective cohort study / follow-up of RCT control patients /derivation of CDR validated on split-sample	Analysis of clinically sensible costs /alternatives; limited evidence reviews/single studies / multi-way sensitivity analyses
	2c	"Outcomes" Research; Ecological studies	"Outcomes" Research	Audit or outcomes research
	3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies
	3b	Individual Case-Control Study		Analysis of limited alternatives/costs, poor quality estimates of data / sensitivity analyses /clinically sensible variations.
C	4	Case-series (and poor quality cohort/case-control studies)	Case-series (and poor quality prognostic cohort studies)	Analysis with no sensitivity analysis
D	5	Expert opinion without critical appraisal/ based on physiology, bench research or "first principles"	Expert opinion without critical appraisal/ based on physiology, bench research or "first principles"	Expert opinion without critical appraisal /based on economic theory or "first principles"

Note: Reproduced (in abridged form) from Levels of Evidence (2009), Oxford Centre for Evidence-based Medicine - downloaded from https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009

To counteract this distortion a new approach has been proposed: the translational strategy needs to utilise findings of *efficacy* and *effectiveness* research and 'translate' into clinical practice. Hybrid study designs have been proposed, containing elements of *efficacy* and *effectiveness* research: studies informed by clinical goals and practice feasibility concerns and trade-offs and compromises are deemed necessary to achieve optimal study design to move research into 'real-world' (Roy-Byrne et al., 2003a)

The evidence synthesis required to strengthen the evidence base should adopt the new research methodology, and critical design issues should be informed by "individual patient data" meta-analysis and mixed treatment comparisons (Sutton, Cooper, & Jones, 2009) - as the challenges to translational research resulting from this interpretation of the E in the EBM are barriers to adoption of new science. Critics put forward that trials and *"other EBM prized methodologies"* include highly selective patient populations, particularly intensive treatment protocols, conducted by expert multi-disciplinary research teams – difficult to replicate or incorporate in routine practice, and clinician behaviour as well as patient outcomes are influenced by a combination of *"multilevel forces"* and therefore tailoring to patient and setting is necessary. Also, real-world translation requires flexibility to deal with pragmatic issues, such as time constraints, system problems, costs, which are almost never captured in studies that make up high-level evidence. (Garfield et al., 2003)

This reasoning should theoretically strengthen the provisions of practicing EMB by integrating critically appraised research results with the clinician's own clinical expertise and with the *"patient's unique biology, values and circumstances"* (Sackett, Strauss, Richardson, Rosenberg & Hayes, 2000), but when referring to how this integration can be made the authors suggest an equally empirical method, by asking the clinician to elicit value judgements from individual patients about the severity of the potentially bad outcomes and

side-effects and corroborate this value judgment with the probability of their occurrence (Number Needed to Treat) to calculate the 'Likelihood of being Helped versus Harmed' Albeit the authors identify this as a useful clinical decision tool that would not require a significant time investment in the clinic (ibid, pg 121) and should be accessible to all clinicians with a working knowledge of basic statistical methods it is in 'real world' doubtful that this is a realistic scenario and makes nor reference to tacit and experiential knowledge of what works.

Further critiques to this integrative concept highlight the *artificial nature* of clinical research being incompatible with actual practice conditions and hence a barrier in knowledge translation (Roy-Byrne et al., 2003); in the pursuit of focus and clinical clarity, randomised controlled trials have rigid inclusion and exclusion criteria and treatment regimens rarely accommodating the diversity of disease progression and comorbidities of the clinical population; surrogate outcome measures for tolerability (such as the rate of discontinuation) are intrinsically unable to capture the acceptability of a particular side-effect in comparison with another.

"Real-world medicine must not only consider the effectiveness of specific treatments, but must do so in the context of patients who have multiple problems and who are often already receiving many different treatments in a setting different from that tested in the trial."(Dans, Dans, Guyatt, Richardson, & Group, 1998)

Whist it is acknowledged that the evidence from a systematic review or a clinical trial is important in the development of a new intervention, the translation of results from a critically appraised trial to an individual patient is described as *"often erratic"* (Simes, 2002) as it does not have the power of being *the only information* needed in the clinical decision-making process. The intervention that showed a benefit in the trial will only be relevant to the clinician and applicable in clinical practice to an individual patient if the design and the outcome of the

trial are directly relevant to that particular patient population and the evidence integrates individual patient characteristics for a *"meaningful risk/benefit assessment"* (ibid., p411)

A further difficulty in translating the 'average effects of a treatment' has been identified by Kent and Hayward (2007): in the drug approval process the FDA/EMEA approach is deemed to be a 'one size fits all' process. Using a single-pre-defined end-point will invariably generate an outcome that would not be generalisable beyond the 'average patient' – which, the authors argue, does not exist beyond the statistical concept (as in the trial some patients would be helped and some would be harmed). Using an adaptive trial design and a contextualised process which would allow for a risk stratified sub-group analyses to highlight different clinical picture and social context variables representing 'real-life' patients would provide a more accurate picture. (Kent & Hayward, 2007)

The emphasis on methodological hierarchy, the assessment of validity based primarily on research design and assumption of generalisability based on dissimilar end-points or surrogate outcome measures may make *classical* EBM an outdated tool.

A critical view of the methodological hierarchy notes that it is a simplistic quantification of the quality of evidence and categorisation may replace the need for individual judgement (Rawlins, 2008) and allocating an RCT a higher grade evidence than an observational study is not always appropriate and sometimes of limited clinical relevance (Concato, 2012; Concato, Shah, & Horwitz, 2000)

Categorising the value of an intervention by the strength of the evidence used to support its effectiveness leaves a challenging gap in the ability to establish the value of interventions where no 'convincing evidence' exists because they cannot be effectively measured.

Practice, in turn, is an invaluable source of information on actual effectiveness of treatment regimens. Advocates of n*aturalistic research* suggest that patient registries and observational studies are a far more appropriate paradigm for capturing patient outcomes (Trotter, 2002). The *medicine-based evidence* approach puts the emphasis on *"clinically relevant issues of who and where were the patients, what an why were the treatments and when and how were the outcomes assessed - as well as an assessment of validity and generalisability considered together and denoted as accuracy"* (Concato, 2012) - reminiscent of the analogy made with the innovation process for mouse traps: why invent a newer and (a matter of opinion) better mouse trap on the assumption of the potentially representative characteristics of a mouse infestation, when the key is to match the teratogenic means to the specificities of *my* mouse problem (Graham, 2012)

Garfield, Malozowski, Chin et al. (2003) identify two phases of knowledge translation, one from laboratory to clinical research and a distinct one from clinical research to clinical practice and highlight a number of complex barriers that coexist to hinder adoption of findings in the real-world and multi-level forces with *"predisposing"*, *"enabling"* and *"reinforcing"* factors (Garfield et al., 2003). They advocate tailoring care to the specific setting and customising to patients, as there is no best-practice standard appropriate for all patients; when generating evidence for a paradigm that has shifted from acute care to chronic conditions, non-randomised study designs and observational studies are more appropriate as they allow the flexibility required to deal with any pragmatic issues that may arise.

In conclusion it can be stated that the move from the primary principles of EBM was simply an evolution of the patterns of clinical care. As care became increasingly coordinated and regulated, the individual clinician decision making process has seen a shift in the last 15 years. The need for an individual clinician to implement in practice results stemming from the

critical appraisal and assessment of the merits, validity and applicability of a paper has been replaced with the organisational implementation of a clinical guideline stemming from the systematic review of the body of knowledge by either NICE /National Collaborating centre or the Cochrane collaboration.

This shift in the responsibility has brought a reprieve from the need to base clinical decisions on integrating *"critically appraised rigorous clinical research"* and calculating the *"Likelihood of being Helped versus Harmed"* (Sackett, Strauss, Richardson, Rosenberg & Hayes, 2000) - much to the relief of clinicians less familiar with the methodological details of *"jitter plots, multiple imputation, negative binomial models, Weibull distributions and inverse probability weighting"* (Concato, 2012) - and allowed the emphasis to shift from research evidence to clinical expertise and patient values.

This is by no means at odds with the methodological virtues of RCTs and systematic reviews of well-designed RCTs with low risk of bias: whilst in the translation from 'bench to bedside' their methodological validity is at the top of the hierarchical model, in the translation from 'clinical research to clinical practice' observational or non-randomised patient centred studies also have a definitive value. It is not necessarily the choice of methodology (quantitative vs. qualitative) that should influence the strength of evidence but the quality of design and conduct with the chosen (most appropriate) study design for answering the clinical question.

In their report on assessing research evidence, Spencer, Ritchie, Lewis and Dillon (2003) propose a framework for assessing the quality of qualitative research and formalisation of quality standards to enable an evaluation of the methodological rigour, soundness and robustness of qualitative research, with a view that it can have a major contributor role in the total body of evidence. The guiding principles are around the *"contributory"* nature of the research in advancing knowledge in a field, the *"defensible design"* and the choice of a method that will answer the research question, the *"rigorous conduct"* by ensuring that the analysis

and interpretation of data is systematic and transparent and the *"credibility of the claim"* by having well-considered argumentation surrounding the significance and generalisability of the findings. (Spenser, Ritchie, Lewis, & Dillon, 2003). This framework is supported by critical appraisal questions (derived from the classical CASP paradigm) which aim to verify the adherence to the principles of rigorous design and conduct and which support the case that qualitative research can be attributed a higher level in the hierarchy of evidence.

In the move beyond clinical epidemiology, where *"medicine is more than the application of scientific rules"* (Naylor, 1995) qualitative studies help in understanding barriers to using EBM and its limitations in informing clinical decisions. By pursuing systematically research questions related to attitudes, beliefs, preferences, it gives a far more accurate picture on how evidence can be practiced to integrate clinical expertise and patient values. Alternative explanatory frameworks came from the *user-led* research agenda: in acknowledging that medicine is practiced in a *"post-modern context"* it recognises the value added by 'evidence' to distinguish between of different treatment options - but challenges its universality, given that it has different value to different stakeholders: *"*[the] *rational, scientific approach to therapeutic decision-making at the core of EBM […]assumes that medical interventions always can be rational and measurable* [but] *patients are left feeling that their concerns are forgotten and that they are little more than a disease being treated"* (Faulkner & Thomas, 2002)

In practical terms, the evidence value is determined by the research question asked: if the question is not relevant to service users, the answer generated will be equally irrelevant. Defining effectiveness as 'symptom relief' may fail to identify aspects that are of significance to the patient and may impact on treatment adherence. User-led research agenda supports research with increased 'ecological validity', a user-defined framework for understanding the

experience of disease *"based on subjective, lived experience […] redefining outcomes according to users' priorities"*, rather than being based on the 'professional concept' of the disease.

However, categorisation involves a degree of subjectivity. The consequentialist approach, where the intrinsic value of an action is assessed by evaluating its consequences (Kerridge, Lowe, & Henry, 1998) is acceptable, if the doctor and the patient agree about the nature of the problem, but does not work where internal experiences, such as quality of life cannot be objectified and easily quantified. (Faulkner & Thomas, 2002)

In conclusion, albeit the need to use 'evidence' and deliver 'evidence-based' care is indisputable, what should count as 'evidence', what value should be assigned to the results of research, and on the basis of what nosological and epistemological context, is still subject of debate. From this perspective, the core principles of EBM are still very relevant, but the integration of research evidence with individual clinician experience and patient values has gained new substance: clinician experience and patient values are no longer subjective, individual and non-descript: they are too to be informed by 'evidence'.

Rycroft-Malone, Seers & Titchen (2004) propose merging external (scientific) and internal (intuitive) approaches and state that the delivery of care should be informed by knowledge resulting from merging sources of evidence: research, clinical experience, patient, client and carer experience, and information on local context and environment (Rycroft-Malone, Seers, et al., 2004). The authors highlight a very useful categorisation of sources of knowledge in each of the participatory element /stakeholder in the decision-making process. Research evidence is acknowledged to be *"dynamic and eclectic"* with *"no such thing as 'the' evidence",* and with multiple interpretations given to its value by each of the stakeholders. Clinical experience at individual level may be *"idiosyncratic, subject to bias, and, as a result,*

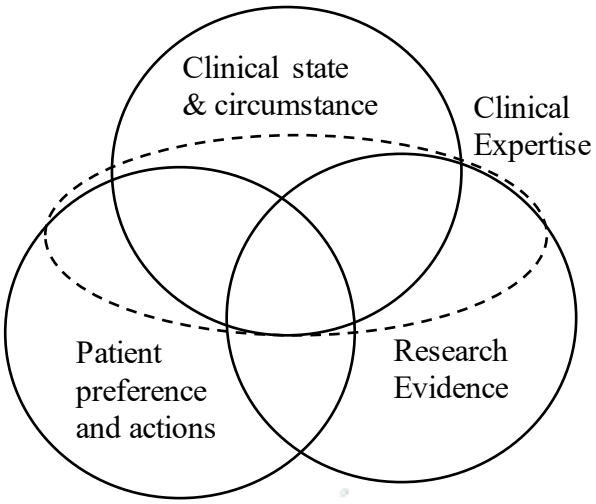
lacks credibility" but knowledge derived from clinical experience gains evidence value. Information on *"practical know-how* can be extracted by 'elicitation', 'articulating and reflecting on practical knowledge' and 'gathering accounts through observation of practice' and then subjected to consensual validation and verification by a body of experts.*"* (Titchen, 2000, quoted in Rycroft-Malone, et al. 2004). This consensus validation by a body of experts is very much in keeping with general principles of care: the Bolam standard applied to the 'standard of care' can be a proxy measure for value when considering existing treatments. It is not clear though how value and what value could/should be ascribed to evidence derived from the clinician or the patient. Neither knowledge derived from clinical experience nor the qualitative investigation of patients and carers views and information about the local context have the required 'level of evidence' to count as a meaningful source for a therapy or prognosis guideline. On the other hand, using this categorisations of *clinical research* as a source of evidence quite distinct from knowledge derived from *clinical experience*, *patient preferences* and *local contextual/environmental information*, removes the onus of circumscribing to a specific 'level of evidence'.

A similar paradigm was earlier proposed by Haynes, Devereaux & Guyatt (2002) but the authors maintain that *"evidence does not make decisions, people do"* and therefore *clinical expertise* has the role of coordinating and integrating *research evidence* and *patient preferences*. (Figure 3) This model made no allowance (apart for 'clinical state and circumstance') for environmental factors and local organisational context but it is very important as a precursor of knowledge utilisation theories as it clarifies the dynamic nature of the decision making process *"decisions may vary from circumstance to circumstance and from patient to patient with the same circumstances"* (Haynes, Devereaux, & Guyatt, 2002) In this model, the factor previously known as 'patient preference has now been divided into two distinct factors, recognising that 'preference' is determined equally by the patient's clinical conditions as well

as by the patient's values. Thus, 'clinical state and circumstances' refers to the patient's condition and the circumstances surrounding his/her treatment seeking behaviour, as a determinant of patient's individual needs, (such as whether a diagnosis has been made, or whether the patient can access treatment) and 'patient preferences and actions' refers to patient values and how strongly those values and beliefs in relation to treatment are likely to be (as a determinant to adherence to treatment).

Figure 3.

Diagram of the updated model of Evidence Based Medicine



Source: based on Haynes, R. B., Devereaux, P. J., & Guyatt, G. H. (2002). Physicians' and patients' choices in evidence based practice. *BMJ (Clinical Research Ed.)*, *324*(7350), 1350.

In both models all factors seem to have the same 'weight' but in reality some factors will weigh more than others and this could be different for individual clinicians; in context, the next logical question to answer is how is the clinical decision made and what are the factors which influence most how (and how much) research evidence and contextual knowledge is used in practice?

Elements of knowledge translation and implementation

> *"As with many interventions intended to prevent ill health, the effectiveness of parachutes* [in preventing major trauma related to gravitational challenge] *has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence-based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute".* (Smith & Pell, 2003)

We know that not all of the research evidence is automatically translated into clinical practice. The gap between evidence and practice has been attributed to many factors, the first of them of them related to the particulars of the individual decision-making process. When a lot of information is available not all of it will be processed in making a decision: the principle of "satisficing" postulates that a limited amount of information will be used to achieve a "sufficiently satisfactory decision". (Bate, Hutchinson, Underhill, & Maskrey, 2012), based on a dual process theory which distinguishes between key processes: a fast, intuitive decision-making system and a system employing deliberate analytical approach. The authors postulate that the discrepancies between evidence and clinical practice occur when individuals rely on the intuitive system processing without activating the analytical system to verify all sources of evidence. The emphasis here is on individual characteristics - such as intellectual aptitude, propensity for logical and critical thinking, education and training - and to a limited degree on the ambient conditions, thus leaving less of a scope for the integration of contextual factors.

I would argue that contextual factors are also important because they may influence or shape whether an individual decision-maker will rely on the intuitive processing or will be

encouraged by contextual patient-related factors and /or by organisational factors to activate the analytical approach.

Knowledge utilisation and implementation research highlights that contextual factors, such as complex organisational structures and cultures, as well as strong professional views have implications for utilisation of knowledge. Healthcare has distinctive features, in which the biomedical science model dominates and therefore shapes our understanding of what constitutes “legitimate evidence” and the authority of the medical profession shapes how that evidence is used. (Dopson, 2005; Dopson, Locock, Gabbay, Ferlie, & Fitzgerald, 2003)

The impact of contextual factors as a “potent mediator” in implementation is supported by the view that evidence is socially constructed and therefore the way in which evidence is perceived by individuals and groups will impact on its successful implementation. A multitude of stakeholders at organisational level may play a positive or negative role in the acceptance or change of guidelines and therefore in implementation and knowledge translation. (Rycroft-Malone, Harvey, et al., 2004)

From the organisational factors, implementation activities are vital to the uptake of a guideline and clinicians display significantly different perceptions of guidelines depending on the implementation strategies, such as a guideline distribution alone vs. local implementation programme (Forsner, Hansson, Wistedt, & Forsell, 2010). Authors highlight that psychiatrists had diverging views about evidence-based practice and raised concerns about guidelines being a means to exert outsider control over their professional practice, as well as about the financial motives that may lay behind the introduction of the guideline; to improve knowledge translation (such as guideline adoption) should therefore ensure that health professionals are actively engaged, and the process takes into account the clinicians’ motivation as well as the contextual factors, such as culture and leadership. Furthermore, clinicians must feel ownership over the process by building collaboratively on existing

strengths and ‘best-practice’ to integrate evidence into routine care, and providing continuity, given that schizophrenia demands a biopsychosocial approach.(Rowlands, 2004)

As the NICE Guidance was supposed to inform service delivery and service development plans, it was expected that its implementation would be built on the National Service Framework for Mental Health (DoH, 1999) and (in England) on the Mental Health Policy Implementation Guide (DoH, 2001), it follows that services would identify best strategies to adopt bearing in mind their skills gap and individual service needs. A review of publications pertaining to schizophrenia guideline implementation highlight three key factors an individual one, i.e. lack of staff skills in this area (which implies that training and supervision would improve implementation), an organisational one, i.e. inadequate management support to facilitate the operational aspects of the guideline implementation, and finally a factor related to service user engagement to ensure that their needs are met (Berry & Haddock, 2008). It is interesting to note that an overview of systematic reviews on interventions aimed at translating research findings into clinical practice concluded that dissemination alone was unlikely to be successful and an implementation plan requires an ‘active’ facilitation strategy to disseminate guidelines, such as teaching, audit, feed-back requests. (Grimshaw et al., 2001).

Based on factors above a number of implementation frameworks have been developed in the attempt to support effective translation of knowledge and its implementation into delivering an evidence-based care.

The domains presented above, i.e. ‘evidence/knowledge’, ‘context’ and ‘facilitation’ have been identified as key elements for translating evidence into practice and developed into a framework (Rycroft-Malone, 2007), building on a framework (PARiHS: Promoting Action on Research Implementation in Health Services) which integrates these factors and proposes

that each is characterised by sub-elements: evidence is made-up by research evidence, clinical experience and patient views; the context is characterised by culture and leadership; the evaluation and facilitation element incorporates roles, skills and attributes. The elements are presented on a continuum (from low to high) and the authors conclude that the higher each sub-element can be marked the more successful the implementation is likely to be. A correlation of variables is also required: *"high evidence"* entailing a match between the robustness of research evidence and the professional consensus and patient needs; similarly, *"high facilitation"* can only be derived from *"high context"* i.e. a culture sympathetic to the prerequisites of knowledge translation and a robust evaluative context.(McCormack, Kitson, Harvey, Rycroft-Malone, & Seers, 2002)

In a comprehensive summative evaluation Damschroder, Aron, Keith et al, (2009) conclude that each theoretical framework of knowledge translation and implementation may be deemed to miss a key construct present in another theory - and a great variability was found in classification, terminology and definitions. The authors proposed a Consolidated Framework for Implementation research by combining constructs presented in previously published theories and eliminating duplicate constructs or those which merely elaborated on points made previously. The framework identifies five major domains that influence the translation of research into meaningful patient care outcomes: "intervention characteristics", "outer setting", "inner setting", "individual characteristics" and the "process of implementation" per se. Within each domain several constructs have been identified to provide a pragmatic structure for approaching the implementation of research findings in a complex context. For example, the characteristics of the intervention are mapped out in relation to the stakeholder's perception of its source, strength of evidence, advantages, costs and complexity; the outer setting relates to patient needs but also peer pressure and external influence such as policy and incentives; the inner setting relates to organisational factors and

a facilitative local culture; individual characteristics circumscribe clinicians; knowledge and beliefs about the intervention and the degree to which they identify with the organisation; finally, the implementation process lists the efficacy of the activities undertaken by the organisation to implement the intervention, such as engaging, appointing formal (or identifying informal) opinion leaders and champions, and reflective/evaluative practices. (Damschroder et al., 2009). As a summative construct, this framework compiles all factors previously identified as facilitators or barriers to knowledge translation. It identifies and classifies in a very well-defined structure the prerequisites for knowledge translation and implementation that stem from all the components of practicing EBM at clinician level - but looks at them from an organisational perspective that was merely touched upon in previous theories as "environmental" and "contextual factors". Key factors identified in previous frameworks (evidence, context and facilitation) and their components (sub-elements) have been re-distributed to be examined form the perspective of their intrinsic characteristics. It is interesting to note that in the theoretical approach the onus has moved from the clinician's responsibility to practice EBM to the organisational responsibility to facilitate the knowledge translation and implementation and components pertaining to an individual level are looked at from an institutional perspective. Whist this thesis will not look at the institutional perspective and will focus its analysis on clinician specific factors, it is important to set a reminder that these are not mutually exclusive factors: clinician attitude can influence organisational culture and vice-versa: an empowering organisational culture will influence individuals' ability to contribute meaningfully to knowledge translation.

CHAPTER II

Do prescribing practices follow the guideline? An analysis of the Prescribing trends for AntipsyChotics in England and Wales, between 2001 and 2014: the PACE study

This chapter is an analysis of the prescribing trends for antipsychotics in England and Wales between 1995 and 2014 with a view of mapping the impact of the change in NICE guidance on clinical practice. The aim of the study was to describe the prescribing patterns before and after the first NICE guideline, the interim period and after the second NICE guideline and to identify whether the prescribing pattern changes to follow the guidance and/or predictions of the published evidence on the efficacy of atypical antipsychotic drugs as first-line treatment in schizophrenia - therefore to test the impact of new evidence and guidance on prescribing.

The null hypothesis of this analysis is one of *no issues* in the implementation of published evidence and guidance on use antipsychotic drugs as first-line treatment in schizophrenia: if the prescribing patterns follow the evidence, the prescribing of atypicals should increase after the 2002 guidance but recede following the published evidence up to 2007 and the guideline revision in 2009.

The study consists of a literature review of published original papers and reports discussing prescribing of antipsychotic agents between 1995 and 2017, and, as the published data was rather sparse, this was followed by a secondary analysis of prescribing data for a period between 2001 (for Wales, and 2006 for England respectively), to 2014. The data shows that neither the change in guideline nor the substantial research evidence published by this time seem to have had an impact on prescribing practice - as the rise in atypical antipsychotic prescribing is not supported by the body of evidence about their comparative effectiveness for the treatment of schizophrenia.

Methodology

The literature review and secondary analysis of prescribing data presented below was conducted at the time the study was initiated - as a necessary first step in setting a methodologically correct research hypothesis, a robust method of exploring anecdotal evidence that antipsychotic prescribing is on the rise.
It is therefore presented as it stood at the time, to enable an apposite view of the contemporary evidence, but update data from more recent publications was integrated where it added significant evidence to the working hypothesis.

The literature search was preformed searching MedlinePlus, PubMed, EMBASE, AMED, CINAHL and PsychInfo databases and the Cochrane library. The search strategy was focused on retrieving original papers and reports discussing prescribing of atypical antipsychotic agents, between 1995 and 2011. The terms used were ‘schizophrenia’, ‘psychosis’, ‘prescri$’ and prescri$ trend$’, ‘NICE’, guidance’, ‘guideline’, ‘implementation’ ‘evidence-base$’, *antipsychotic’, ‘neuroleptic’, ‘SGA’, ‘FGA, ‘typical’, ‘atypical’, drug generic name*, drug trade name* and appropriate MESH terms Antipsychotic Agents/classification; Antipsychotic Agents/economics; Antipsychotic Agents/therapeutic use*, Drug Costs; Drug Prescriptions; Drug Utilization Review*; Health Services Research; Humans; Practice Patterns, Physicians'/statistics & numerical data; Practice Patterns; Physicians'/trends; Primary Health Care/statistics & numerical data*; Primary Health Care/trends; Pharmacoepidemiology; United Kingdom - in the title, abstract, subject headings, heading word, keyword.
All relevant studies from the reference lists were followed up.
The search retrieved 114 papers out of which 38 were database duplicates, 12 discussed antipsychotic prescribing in children and adolescents (therefore for indications outside the scope of the Guideline) and 6 papers described antipsychotic prescribing in local hospital setting/emergency wards; 18 papers discussed issues of metabolic monitoring in prescribing antipsychotic medication, one was a review of pharmaco-epidemiological studies exploring

drug prescribing trends; a further 27 studies discussed prescribing patterns outside the UK or for indications other than schizophrenia – an these contributed understanding the general context but were not included in the review. The remaining 13 papers[5] made the object of the review and one of the sources of data for the results presented below.

Prescribing data (British National Formulary Section 4. Antipsychotics, Subsection 4.2.1 and 4.2.2) was requested from The NHS England Information Centre, Prescribing Support Unit and The NHS Wales Informatics Service (formerly Health Solutions Wales) Prescribing Services. The data was requested in Defined Daily Doses (DDD) for Quarter January 2001 to Quarter December 2014. As a choice of measure DDD was used to enable standardisation of comparative usage across the time-line, between various drugs. The WHO Collaborating Centre for Drug Statistics Methodology defines DDD as the "*assumed average maintenance dose per day for a drug used for its main indication in adults"* (World Health Organisation Collaborating Centre for Drug Statistics Methodology, n.d.). Standardising drug use to a unit equivalent to 'one day's worth' of treatment enabled to assess the trend in overall drug consumption over time. The other advantage with using DDD is that changes in prescribing patterns due to other indications for antipsychotic use, (e.g. affective disorders), would have less impact as these utilise much lower daily dosages than those defined for schizophrenia. This important primary data enabled to expand on the published work and have a broader view on the prescribing trends. Data received was presented on a line listing for each preparation of each drug, both the generic and the proprietary brands as dispensed (e.g. Abilify_Oral Soln 1mg/ml; Abilify_Orodisper Tab 10mg; Abilify_Orodisper Tab 15mg; Abilify_Tab 10mg; Abilify_Tab 15mg; Abilify_Tab 30mg; Abilify_Tab 5mg; Aripiprazole_Oral Soln 5mg/5ml; Aripiprazole_Orodisper Tab 10mg S/F;

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[5] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Aripiprazole_Orodisper Tab 15mg S/F; Aripiprazole_Tab 5mg; Aripiprazole_Tab 10mg; Aripiprazole_Tab 15mg; Aripiprazole_Tab 30mg, etc) aggregated for each yearly quarter. The initial set of data was limited to December 2010 and a subsequent request released data up to 2014. As England and Wales have two distinct NHS Informatics Service, two sets of data were received, one for England, one for Wales. This however, was not necessarily a limitation, as it allowed the analysis to follow distinct time points (after the issue of the first guideline, the interim period and after the issues of the second guideline). The data analysis involved pivotting tables to ensure that alphabetical listing for proprietary drug (brand name) was included in the final computation with the generic preparation (for example, although Atrolak was listed under A, and Seroquel under S, it was computed appropriately with the rest of quetiapine preparations), i.e. was pivoted by BNF subsections to include all doses of proprietary and non-proprietary preparations and 'quarter ending' to analyse the comparative use over time in total DDD, as well as a percentage of specific drugs from total prescribing. The results of the data analysis have been integrated with the findings of the literature review to either support arguments made by published literature, or to document findings where published data was sparse.

Results

The results of a systematic review of pharmaco-epidemiological studies discussing antipsychotic prescribing between 1995 and 2009 show an overall increase in the annual use of antipsychotic medication internationally (before our cut-off point at which the guideline was issued in 2002), and highlights a noticeable increase in antipsychotic prescribing globally since the introduction of atypicals (Verdoux, Tournier, & Bégaud, 2009). The authors retrieved eleven studies matching the inclusion criteria – sample recruited in the general population to reflect real-life conditions of use, excluding studies conducted on clinical samples. This is consistent with the general outlook of the guideline (i.e. prescribing in primary care rather than in specialist psychiatric units). The analysis included prevalence and incidence rates, as well as prescribing data, and shows a four-fold increase between 1985 and 2000 in total antipsychotic prescribing in Spain (due mostly to increase in atypicals as the typicals prescribing seems to be constant from 1993), a 38% increase in Canada between 1992 and 1998, a 14% increase in Australia between 1995 and 2001, a 44% increase in atypicals prescribing USA between 1989 and 1997. The authors acknowledge that a publication bias may have occurred in reporting preponderantly studies that show an increase in prescribing, and the majority of studies do not provide information on diagnostic related use, but the review is helpful as it allows to see UK prescribing in global context.

There are only two studies looking specifically at the prescribing trends for antipsychotics in the UK covering this time period, and most of the information synthesized below comes from the NICE Technology Appraisal 43 Implementation uptake reports (2006; 2008) which supports the findings of the studies. The reports quantified the implementation of the first guideline by mapping the use of atypical antipsychotics as a proportion of total antipsychotic prescribing, as a *"measure of overall uptake",* between 2000 and 2006 and 2007 respectively. Atypical antipsychotic prescribing, as a proportion of total antipsychotic

prescribing, rose from 21% in quarter ending January 2000 to over 67% in quarter ending March 2007, with a reciprocal decrease in FGA prescribing. (NICE, 2006, 2008). Plotting the data demonstrates a constant increase in the number of prescriptions for atypical antipsychotics dispensed in England in this period and has a few interesting characteristics (Figure 4). The total rise in antipsychotic prescribing is not featured, as the graph shows the proportions of typicals and atypicals in total prescribing; what is shown is a sudden increase in atypical antipsychotic prescribing from 25% to over 45% between quarter ending December 2000 and quarter ending December 2001, and a continuous rising trend to 62% in quarter ending March 2004. The NICE guideline CG1 was published in June 2002 and is positioned on the graph in the middle of this rising trend. It is therefore an assumption that the NICE guideline had an impact on the prescribing trend as it is not possible to distinguish based on this information whether the trend was following a 'natural evolution' or has been given an impulse by the guideline. Moreover, a trend was in progress before the guidelines were published, and no discernible impact on the rate of that trend can be seen.

The papers presenting data before the introduction of the guideline support this hypothesis: a study examining psychotropic medication use throughout the Mental Health Services in England in relation to the introduction of the first National Service Framework, identifies changes in service patterns and outcomes, and lists a tenfold increase in antipsychotic prescribing between 1996 and 2002 and raises concerns over the appropriateness of this prescribing (Knapp, Kanavos, King, & Yesudian, 2005). The data is consistent with data resulting from smaller local studies with the same period quoting a 28% growth in prescriptions in Scotland between 1994 and 1997 – with 90% of it being accounted for by prescribing risperidone, sertindole, olanzapine, clozapine and quetiapine (Stark, Jones, Agnew & Hepburn, 2000), a sixfold increase in West Midlands between 1996 and 2001 – with most of in accounted for by the 45% increase in olanzapine and 38% in risperidone

prescribing, and a 24% decrease in typicals (Ashcroft, Frischer, Lockett, & Chapman, 2002) and, over the same period a twentyfold increase in expenditure in Greater Manchester (Hayhurst, Brown, & Lewis, 2003), justified possibly by a switch from inexpensive typicals to more expensive atypicals. However, at the time of its publication, the NICE Technology Appraisal 43 guidance assumed that the atypicals would reach 65% of total prescribing and this was used as a guideline for monitoring the uptake / implementation.

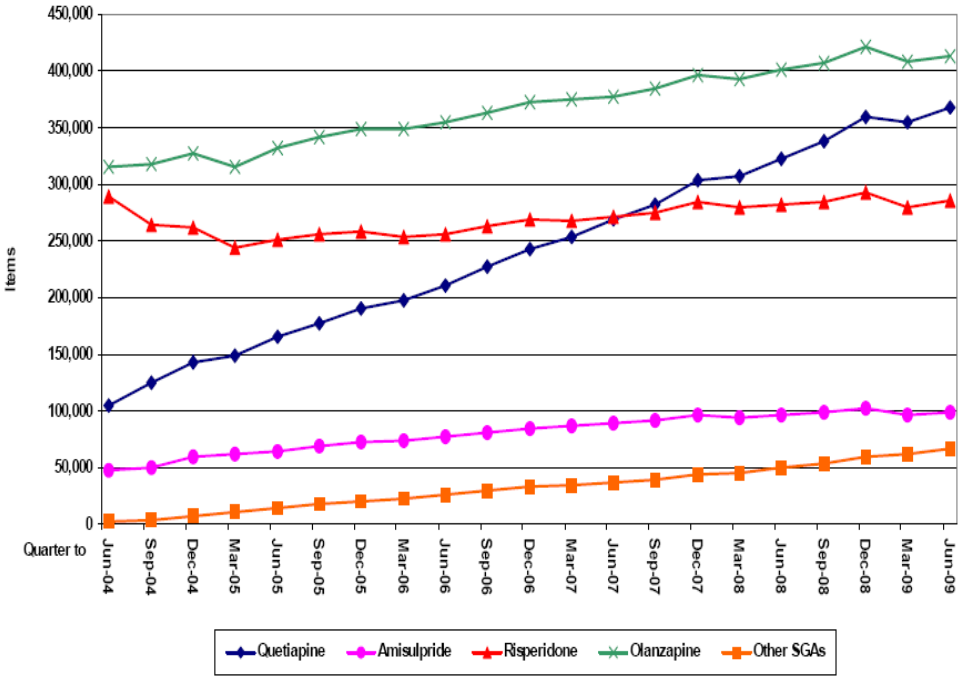
The results of a population based observational study using the General Practice Research Database by Kaye and colleagues (2003) identifies a 16% increase in the annual use of antipsychotic drugs between 1991 and 2000 – from 10.5/1000 to 12.5/1000 - and attribute this to an increasing average duration of treatment. The authors also identify an increase in the use of atypical antipsychotics (olanzapine and risperidone) and a matching decrease in use of flupentixol, chlorpromazine, trifluoperazine and fluphenazine (Kaye, Bradbury, & Jick, 2003) on the background of an increase in use of antipsychotic drugs to treat non-psychotic disorders, supported by evidence that whilst the rate of fist–time antipsychotic drug use had a gradual increase in the 10-59 year olds, the curve raised sharply in the 60-99 year old groups.

The NICE implementation uptake reports name olanzapine as the most commonly prescribed drug, followed by risperidone and quetiapine. A drop in risperidone prescribing is identified starting with quarter ending March 2004. A breakdown analysis of individual drugs prescribing conducted in 2009 by the National Prescribing Centre shows an increase of nearly 50% in atypicals prescribing and a decrease of 15% in typicals prescribing between March 2004 and March 2009: quetiapine has a significant proportion in this rising trend, from 100,000 items in 2004 to over 380,000 items in 2009, followed by olanzapine (from 320,000 to 420,000 items) and amisulpride (with a 100% increase from 50,000 to 100,000 items).

Notably, the prescribing trend for risperidone decreased from March 2004 to March 2005 by over 20% (280,000 items), presumably following the MHRA (March 2004) warning on increased risk of stroke (Schizophrenia Data Focussed Commentary. The National Prescribing Centre, 2009). Although this data is difficult to corroborate with the Prescription Cost Analysis primary data (as it is presented in the publications in *items* rather than in DDD), it helps to confirm the hypothesis that a significant proportion of low dose SGA - and risperidone in particular - would have been used off-label for treating mood disorders and agitation in dementia and psychosis in PD. The MHRA class warning may have also resulted in an increase in low dose Quetiapine prescribing (Figure 5).

Figure 5.

Trends in the prescribing rates of individual oral atypical antipsychotics in general practice in England between 2004 and 2009



Source: National Prescribing Centre (2009) *Schizophrenia: Data-Focussed Commentary*., The Health Foundation. http://personcentredcare.health.org.uk; reproduced under Creative Commons License © The Health Foundation, 2009

One potential explanation for the prescribing trends, would be supported by the rise in Quetiapine (one of the first SGAs to get an affective disorder licence), and the lower dosages used. A threefold increase in quetiapine use may be driven by this affective disorder usage,

however, there is only a 30% increase in olanzapine usage, which also had licences in this area. Amisulpiride use doubles, even though it doesn't have affective disorder licence. Similar results are shown by King and Knapp (2006) who used the same General Practice Research Database to look at atypical antipsychotics prescribing and concluded that it grew between 1993 and 1999 from 1.8% to 20.8% as a proportion of antipsychotic prescribing. The authors looked at the records of 4,391 patients and identified factors associated with the selective prescribing of atypicals: younger patients were more likely to be prescribed an atypical, as were patients with a history of hospitalisation in the previous year or with frequent (six or more) visits to the GP (King & Knapp, 2006). This is supported by the findings of an earlier survey of antipsychotic prescribing which included data on 2012 patients from thirty-six inpatient units and which showed a 28.6% use of a antipsychotic polypharmacy and an incidence of 19% in use of high-dose atypicals, where co-prescription tended to be more prevalent in patients aged 40 years and over (Mace & Taylor, 2005).

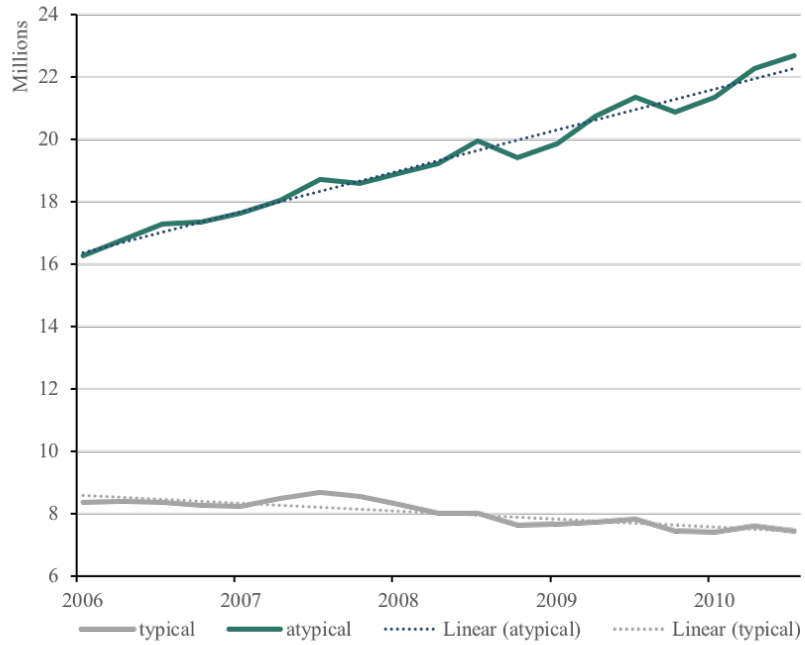
Livingston (2011) describes in a prescribing review a 24% increase in the antipsychotic prescribing in the past 5 years – with an associate cost increase of 18%. This is attributed to a higher prescribing of atypicals, accounting for 76% of volume and 95% of costs of total antipsychotic prescribing. However, if there was a 24% increase in overall antipsychotic prescribing, and a shift towards SGAs, a cost increase larger than 18%, would be expected, given SGAs are far more expensive (by an order of magnitude) than FGAs. The author also confirms a decrease in prescribing for the top three typical antipsychotics (chlorpromazine, haloperidol and trifluoperazine) by 10% (to a total of 20% of prescribing) and an increase in prescribing of olanzapine (to 32%), quetiapine (to 31%) and risperidone (to 31%). This increase is attributed to the recommendations of the NICE guideline CG82 to consider the risk of dyskinesia and potential for metabolic disorders when selecting the choice of antipsychotic – albeit recognising the fact that the lesser propensity of atypical antipsychotics to cause movement disorders may be attributed to flawed data in trials

(comparing them to doses of haloperidol likely to induce movement disorder) rather than to an inherent property of the atypicals. However, the use of SGA to avoid metabolic disorders would really be flying in the face of evidence.

The analysis of prescribing data confirms the increasing atypical antipsychotic prescribing trend despite new evidence and revision of the NICE guideline. The total antipsychotic prescribing increased by 22.8% between June 2006 and December 2010 (from 22,955,343 to 28,196,493 DDD). As a percentage of total prescribing, the rise in atypical antipsychotic from 66% in June 2006 to 75% (quarter ending December 2010) may not appear to be as sharp an increase as previously thought (Figure 6 and Figure 7).

Figure 6.

Antipsychotic prescribing (England and Wales) between 2006 and 2010 (in DDD)



Source: Prescription Cost Analysis data (NHS England Business Services Authority, NHS Wales Informatics Service, June 2011)

However, the total atypical prescribing in England grew from 15, 151, 355.41 DDD in quarter ending June 2006 to 21,187,037.44 DDD in the quarter ending December 2010, which is an increase of nearly 40% in atypical prescribing (Table 5). This may be largely attributable to a marked increase in quetiapine (123% increase) and aripiprazole (224% increase) prescribing. (Table 6).

Table 5.

Increase in antipsychotic prescribing (in DDD) in England June 2006 to December 2010

	Jun-06	Dec-10	% increase
atypicals	15,151,355	21,187,037	
% of total prescribing	66.00	75.14	39.8%
typicals	7,803,988	7,009,456	
% of total prescribing	34	25	-10.2%
total	**22,955,343**	**28,196,493**	**22.8%**

Source: Prescription Cost Analysis data (NHS England Business Services Authority, 2011)

Table 6.

Disaggregated analysis of prescribing trends in England (by preparation, in DDD) June 2006 to December 2010

	Jun-06	Dec-10	% increase
Quetiapine	1,996,853	4,462,677	123%
Amisulpride	1,281,321	1,509,155	18%
Risperidone	3,322,721	3,844,989	16%
Olanzapine	7,952,493	9,495,330	19%
Aripiprazole	569,294	1,841,860	224%
other SGA	28,674	33,027	15%
total	**15,151,355**	**21,187,037**	**40%**

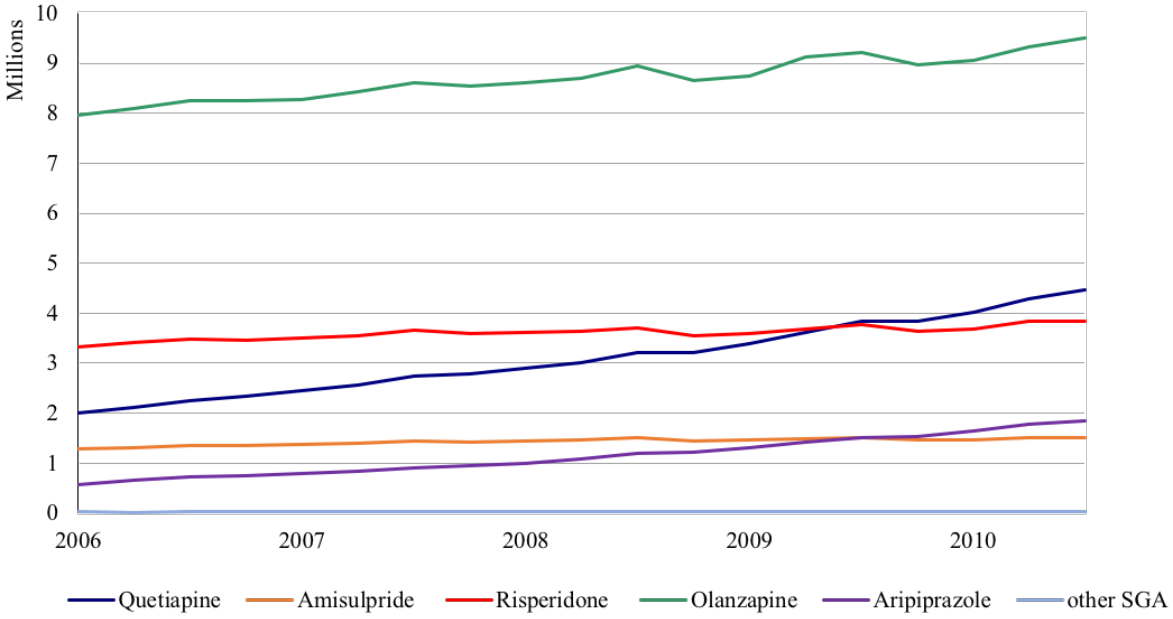
Source: Prescription Cost Analysis data (NHS England Business Services Authority, 2011)

An equally significant contributor to the total increase may be olanzapine prescribing, albeit with only an 18% increase but a very large proportion of the total prescribing 9,494,333 DDD in quarter ending December 2010. It is noteworthy that the expiry in 2007 of the patent for oral risperidone and availability of generic versions at a better pricing structure and the licensing in 2008 of low-dose risperidone for short-term use in treating persistent aggression in patients with moderate to severe Alzheimer's disease did not result in a significant increase

in its prescribing in comparison with other atypicals and the overall trend (Figure 8). This is an interesting observation, as we would have expected a significant shift in SGA prescribing towards risperidone. This suggests that cost was not an important factor driving prescribing (and this would be explored in a subsequent qualitive study of factors influencing prescribing). An other interpretation is that the rise in SGA prescribing is driven predominantly for other indications (e.g. affective disorder), for which risperidone did not have a licence.

Figure 8.

Disaggregated analysis of prescribed atypical antipsychotic in England between 2006 and 2010 (in DDD)



Source: Prescription Cost Analysis data (NHS England Business Services Authority, 2011)

The publication and dissemination of the findings of two large-scale safety and efficacy studies does not seem to have made an impact on the overall atypical prescribing trend. The NIMH funded Clinical Antipsychotic Trials of Intervention Effectiveness trial, 2006 (CATIE trial); Comparison of Optimal Antipsychotic Treatments for Adults With Schizophrenia, 2008; Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study, 2007 (CUtLAS Study) which suggested that second generation antipsychotics did not make a significant

difference in quality of life measures or schizophrenia symptoms when compared to first generation antipsychotics; the comparison of other outcome measures (patient satisfaction and 'overall cost of care') were similar, and rates of extrapyramidal side-effects, tardive dyskinesia, and akathisia did not differ significantly.

So far, the published literature shows that overall antipsychotic prescribing is on the increase but atypical antipsychotic prescribing increase is more significant than the increase in typicals. Despite new evidence and guideline revision, it seems that evidence does not translate into changes in prescribing trends. NICE Guidelines do not appear to have significantly altered the atypicals prescribing trend; major publicly funded trials results (CATIE and CUtLAS) had no significant impact on prescribing trends.

A safety warning issued in March 2004 by the MHRA (The Committee on Safety of Medicines (CSM - the predecessor to the Commission on Human Medicines) regarding the increase in the risk of stroke with the use of risperidone or olanzapine in elderly people with dementia) coincides with a substantial decrease in risperidone and olanzapine prescribing, however, a subsequent 2005 Europe-wide review (concluding that this risk could not be excluded for other antipsychotics (atypical or typical), and the product information for all antipsychotics was updated to include a class warning) and a renewed CSM warning in October 2007 had no impact on the prescribing trend (which shows an increase in SGA prescribing).

The analysis of prescribing data supports the conclusions of the reviews: a 22.8% increase in total antipsychotic prescribing between June 2006 and December 2010, and a rise in SGA from 66% (June 2006) to 75% (Dec 2010) as a percentage of total antipsychotic prescribing.

The prescribing behaviour appears to favour atypical antipsychotics, despite revised guidelines, differences in costs and side-effects. This increase may be largely attributable to a marked increase in quetiapine (123%) and aripiprazole (224%) prescribing. An equally significant contributor to the total increase may be the olanzapine prescribing, albeit with

only an 18% increase but a very large proportion of the total prescribing 9,494,333 DDD (quarter ending Dec 2010). The expiry in 2007 of the patent for oral risperidone, the availability of generic versions at a better pricing structure and the licensing in 2008 of low-dose risperidone for short-term use in treating persistent aggression in patients with moderate to severe Alzheimer's Disease did not result in a significant increase in its prescribing, in comparison with other atypicals and the overall trend.

This trend continues even after the period of implementation of revised Clinical Guideline which removes the previous emphasis on prescribing atypicals. The combined figures for England and Wales for the subsequent for which data became available (up to December 2014) illustrates better the consistent year on year increase in atypicals, so that at end of study period they make up 79.9% of total antipsychotics prescribed (Figure 12).

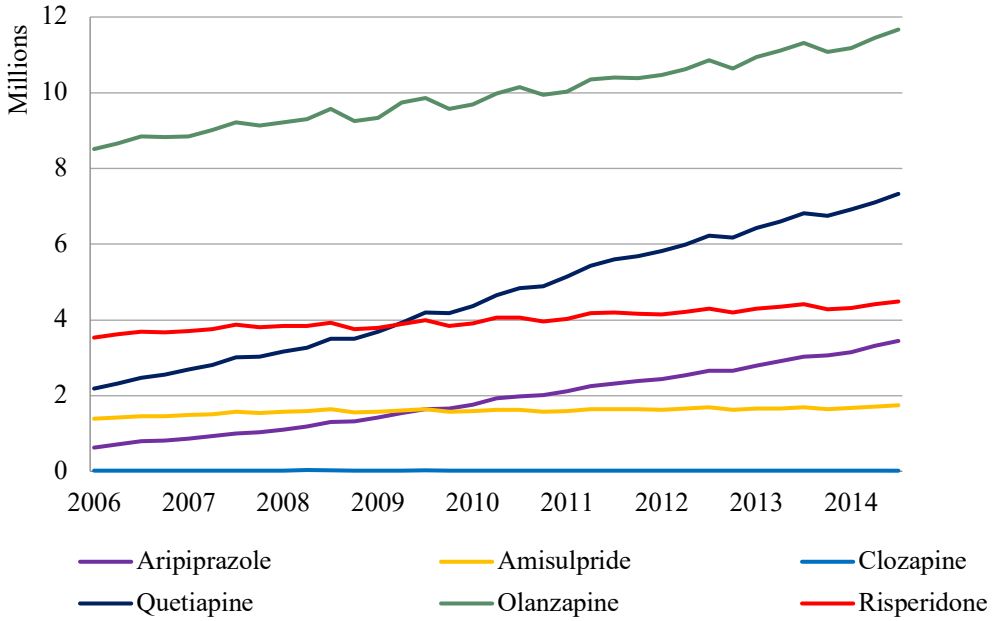
The largest increase is in Quetiapine, by more than 18 million DDD between 2006 and 2014, although this may be attributed more to its use in managing mood disorders, given it limited clinical efficacy in comparison to other antipsychotics (Leucht et al., 2013). There is a small increase in Clozapine prescribed over the study period of (3,454 DDD), but despite the strong evidence for its high efficacy, Clozapine only makes up 0.1% of the atypical antipsychotics both in 2006 and 2014. Olanzapine prescribing also rises (14%) from 10,150,300 DDD in December 2010 to 11,668,970 DDD in December 2014 (Figure 9).

Concomitantly, the prescribing of typicals decreases, with chlorpromazine and trifluoperazine decrease contributing most to the decline (Figure 10). One possible explanation is that the withdrawal of Mellaril may have generated a lot of caution over phenothiazines (e.g. chlorpromazine) and in may have resulted in it being replaced with risperidone especially for treating challenging behaviour in LD ((Davies, Cooke, Moore, & Potokar, 2002).

At the end of the study period, Zuclopenthixol is the most popular typical, with 5,244,935 DDDs being prescribed in 2014.

Figure 9.

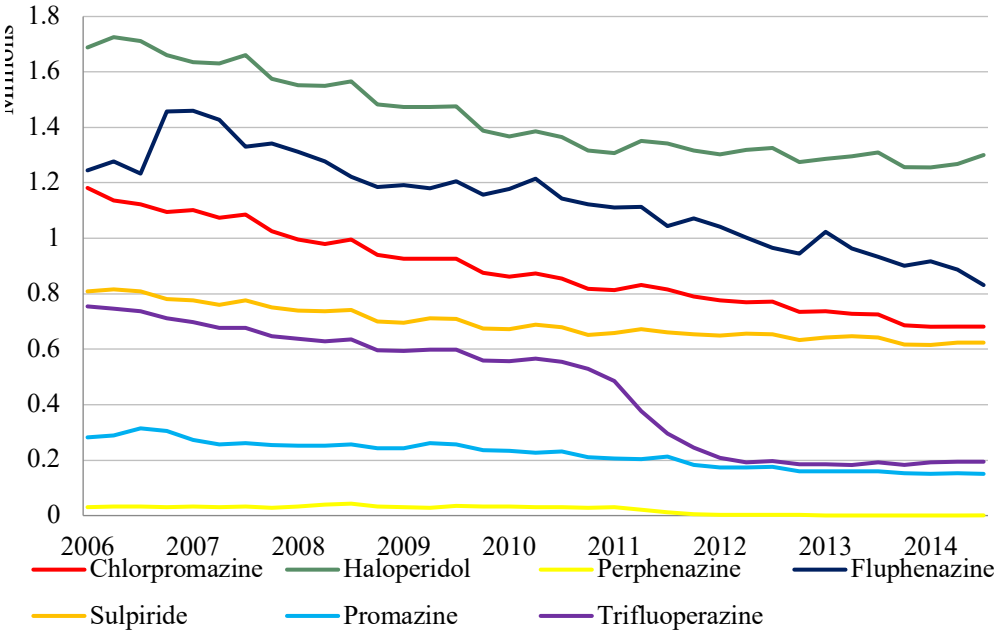
Disaggregated analysis of atypical antipsychotics prescribed in England and Wales between 2006 and 2014 (in DDD)



Source: Prescription Cost Analysis data (NHS England Business Services Authority, NHS Wales Informatics Service, June 2011; June 2015)

Figure 10.

Disaggregated analysis of typical antipsychotics prescribed in England and Wales between 2006 and 2014 (in DDD)

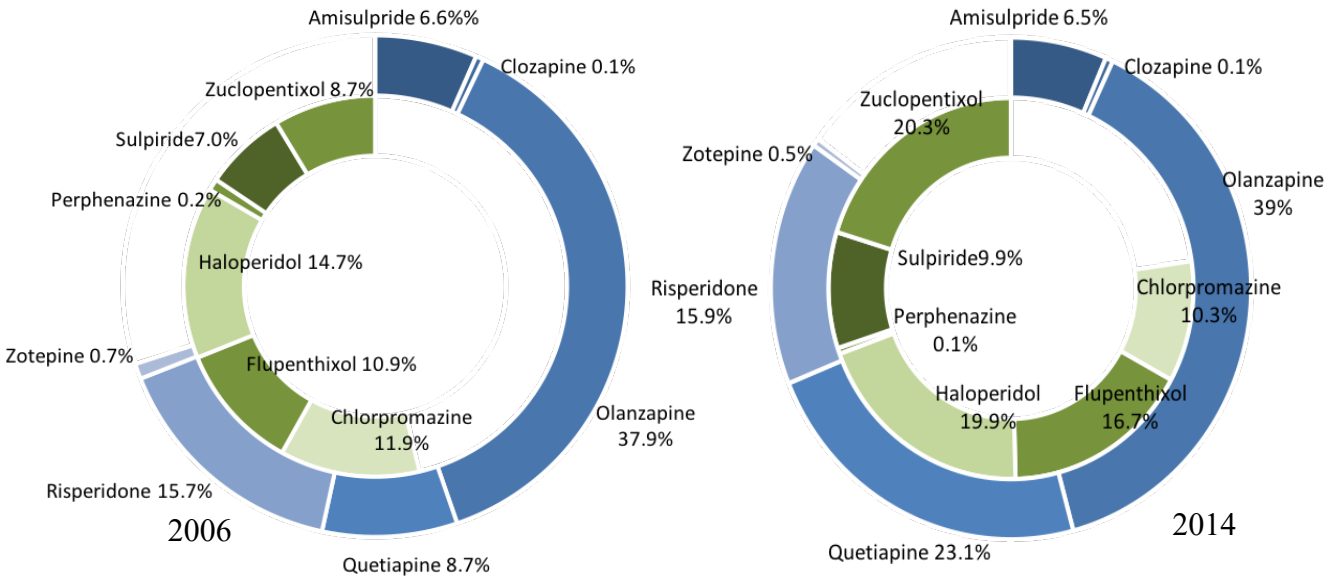


Source: Prescription Cost Analysis data (NHS England Business Services Authority, NHS Wales Informatics Service, June 2011; June 2015)

As a proportion, the greatest increase is seen in Zuclopentixol and Quetiapine (Figure 11), but there are no dramatic reductions in any of the individual antipsychotics, which suggest they these increases are replacing other, less frequently prescribed antipsychotics.

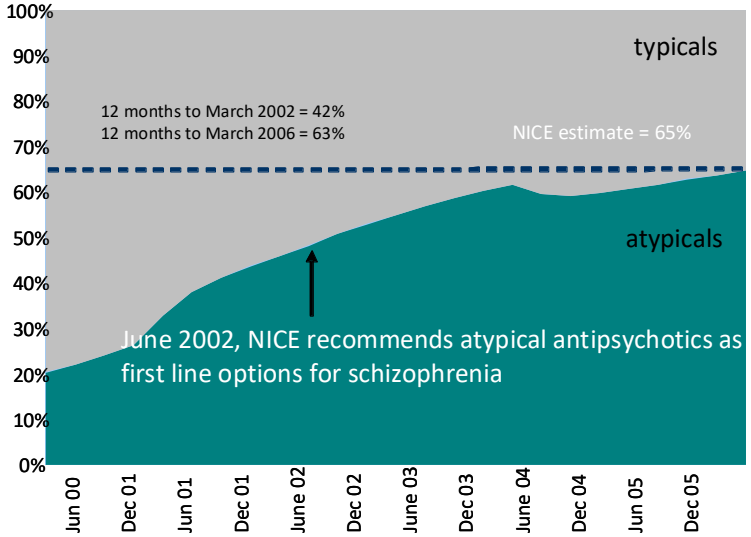
Figure 11.

Comparative proportion of typical/atypical antipsychotic prescribing 2006 to 2014



Source: Prescription Cost Analysis data (NHS England Business Services Authority, NHS Wales Informatics Service, June 2011; June 2015

Figure 4. *Rise in atypical antipsychotic prescribing between 2000 and 2006*



Source: TA43 - NICE Implementation Uptake Report: atypical antipsychotic drugs for the treatment of schizophrenia (NICE, 2008)

Figure 7. *Typical/atypical antipsychotics as a proportion of total antipsychotic prescribing (England and Wales) between 2006 and 2010*

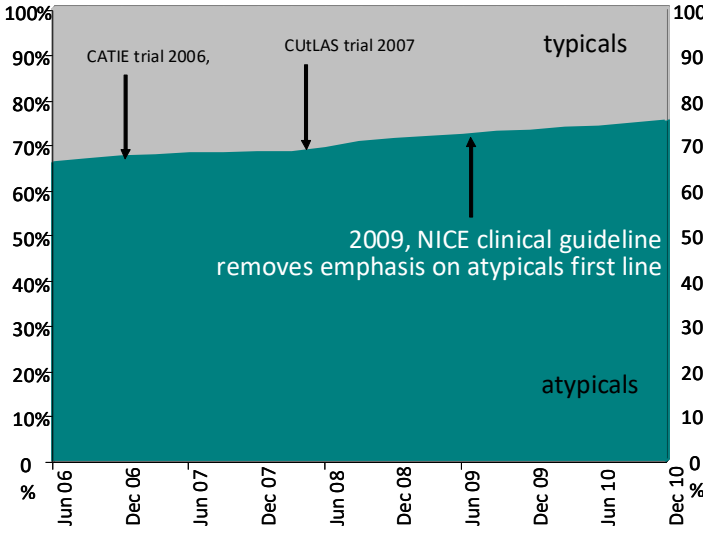
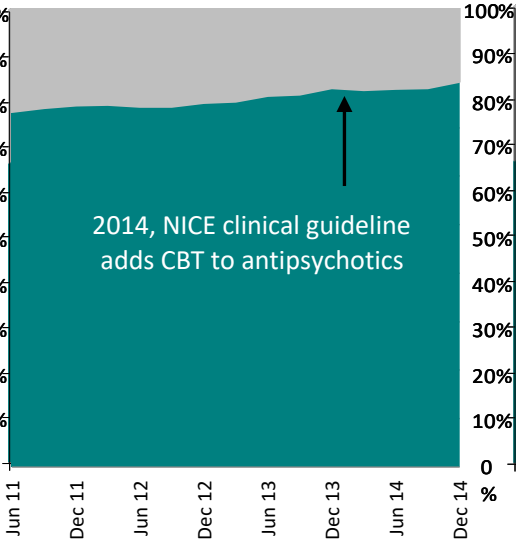


Figure 12. *Rise in atypical antipsychotic prescribing between 2006 and 2014*



Source: Prescription Cost Analysis data (NHS England Business Services Authority, NHS Wales Informatics Service, June 2011; June 2015)

Discussion

These results highlight important aspects relating to guideline implementation and knowledge translation. An increasing trend in atypical antipsychotics prescribing seen before the Clinical Guideline 1, continues despite the change in recommendations following the introduction of the Clinical Guideline 82 in 2009, and the trend does not show signs of decrease after the revision in Clinical Guideline 178.

Furthermore, the prescribing trends show no association with further research evidence. This lack of knowledge translation is illustrated by the smaller than expected increase in clozapine use. Its research evidenced efficacy may have given way to apprehension of potentially fatal agranulocytosis and the increased burden of rigorous monitoring. The introduction of depot Paliperidone and Lurasidone, may also have provided more options. Olanzapine and quetiapine have seen the biggest increase in proportion.

Olanzapine is the prevalent antipsychotic and its prescribing has seen a consistent increase, despite its propensity for metabolic side-effects and weight gain. The introduction of depot preparations and improved metabolic monitoring may have led to an increased confidence in the ability to safely prescribe it and manage the associated side effects. However, the increase seen with Olanzapine remains a worrying trend given that metabolic syndrome is associated with a 2-fold increase in mortality (McGrath, Saha, Chant, & Welham, 2008).

The rise in Quetiapine prescriptions follows the same increasing trend, although its clinical efficacy is reduced in comparison to clozapine, amisulpride, olanzapine, risperidone and paliperidone – maybe due to its increased use for the treatment of mood disorders.

The increase in prescribing atypical antipsychotics is matched by a decrease in prescribing typical – again in contradiction with research evidence: the biggest reduction can be seen in the prescribing of Haloperidol, which is placed 8th in the hierarchy of clinical efficacy, ahead of quetiapine). Given its association with high rates of extrapyramidal side-effects its

reduction in use could be attributed to increased patient awareness/refusal to the risks, but also to possible clinician factors. In the aftermath of NICE guidelines, an increased prescribing of atypicals meant diminishing clinical experience with typical antipsychotics which would mean that individual clinicians would not be comfortable advocating their use or treating the side effects. Conflicting information between guidelines may have led to a degree of uncertainty for practitioners.

Limitations

Very few published studies explored specifically the uptake of the NICE guidance for schizophrenia, and the reports received could not be ascribed a 'level of quality' of evidence. Data on the uptake/implementation of the NICE guideline is scarce and few peer-reviewed publications exist - a significant proportion of the papers are reports by NHS/PCT, NICE, NPC data focused commentary, etc. All papers seem to have distinct scales of measuring antipsychotic prescribing (e.g. number of "items", number of "individuals", "cost", etc). Furthermore, the source data for these reports is the Prescription Cost Analysis (PCA) system generated by the Prescription Pricing Division of NHS Business Services Authority in England. PCA is based on prescriptions dispensed in the community by pharmacists and dispensing doctors in England, but includes items prescribed in Wales, Scotland and Northern Ireland, Isle of Man and dispensed in England. It does not include prescriptions issued and dispensed in hospitals and this may reach levels of significance in acute care and Mental Health NHS Trusts, where a proportion of patients treated for schizophrenia could be inpatients at any point of time. However, the majority of prescriptions are issued in primary care, which will also reflect secondary care practice as GPs will tend to continue treatments initiated by specialists.

An additional source of data mentioned in some papers was the General Practice Research database - which introduces a selection bias to participating GP practices. Admittedly, the GPRD has seen since 1994 an improvement in the quality of data and a growth in the number of practices contributing data but at the time of this analysis the dataset covered only approximatively 8% of the UK population. [6]

All papers identified during the initial stages of the study discuss prescribing trends up to 2007, and therefore no published data on the impact of the change in guideline in 2009 exist. This led to the need to retrieve and analyze antipsychotic prescribing data to cover the missing period (2007-2010) in order to develop a working hypothesis.

Furthermore, all papers identified present data without differentiating for dose, indication or administration route, or do not have standardised diagnostic assessment, and it is therefore difficult to estimate/quantify/describe the impact of NICE guideline, safety warnings, licensing for other indications, end of patent and generics becoming available. It is not possible to quantify how much of the prescribing was within the scope of the guideline (first-line treatment of schizophrenia in adults – as a replacement for typicals that controlled the symptoms but caused intolerable side-effects) and what percentage was used in children and adolescents or prescribed for other indications (atypical antipsychotic drugs have been licensed for short term use - or used off label - as mood stabilisers in dementia, treatment / prevention of mania in bipolar disorder, etc.). This has been prescribing practice for a long time, so one would expect minimal changes over this time period. The biggest change is likely to have occurred from the additional indication for quetiapine and olanzapine in the

[6] GPRD dataset description downloaded from http://www.gprd.com/products/database.asp on 09/09/2011

treatment of bipolar disorder, and its off-label uptake as an augmentation in treatment of depression.

There is evidence that antipsychotics are frequently prescribed 'off-label', for indications for which they have not had regulatory approval (Verdoux et al , 2009, Alexander, Gallagher, Mascola et al, 2011) but a review of Prescription Cost analysis data between 1998 and 2010 by Ilyas and Moncrieff (2012) shows an increasing trend for drugs typically classed as mood stabilisers from 2006.8 (thousand items) in 1998 to 3680.5 (thousand items) in 2010 – a mean change per year of 7.4% from baseline – which would reinforce the hypothesis that only a minimal increase in antipsychotic prescribing was due to off-label prescribing – with the proviso that authors recognise that the mood stabilisers have been categorised might be imprecise, since this is not a category used in the Prescription Cost Analysis

In addition to the off-label prescribing, there has been a widening of licenced indications for some antipsychotics which are now licensed for the treatment of bipolar disorder.

This may account for some of the increased antipsychotic prescribing, particularly as this would have had a sustained 'awareness raising' campaign by the pharmaceutical industry but Ilyas & Moncrieff (2012) argue though that it seems unlikely that the increase can be accounted for by prescribing for this relatively rare condition and more lliely other factors may have contributed more, such as longer duration of use in schizophrenia and psychosis, including earlier initiation of treatment associated with early intervention services.

The limitations originating from the lack of data on the clinical indication for which the drug, was prescribed and whether this may have been off-label is also acknowledged in the report on use of NICE Appraised Medicines in NHS in England (Health and Social Care Information Centre, 2011). This statistic is generated as a proxy measure for implementation uptake by providing data on prescribing of various drugs in relation to their predicted use, after the issue of their respective NICE appraisal. In the chapter dedicated to atypical

antipsychotics no figures have been made available, only a statement to the effect of the limitation of the available prescribing data, clarifying that is not possible to give an estimate of use in schizophrenia, in the absence of data to corroborate prescribing to diagnostic, given the range of indications which are have not been the subject of the guideline. The report also acknowledges that different drugs may be used and dose titration is common before reaching therapeutic efficacy, therefore it is not possible to generate clear data on implementation uptake (ibid. pg.103)

This limitation is also valid for the data retrieved from the Prescription Cost Analysis: the lack of corroboration of prescribing data with diagnostic indication means that the trend identified cannot be attributed solely to prescribing for schizophrenia and therefore to the guideline. In its current format, the data in Prescription Costs Analysis system is not linked to individual patient details (age, gender, prescribed indication). Therefore, it is safe to assume that a certain proportion of the prescribing has been made for indications outside the scope of the schizophrenia guideline. To mitigate for this, data relating to prescribing of doses unlikely to be prescribed for schizophrenia has been removed for the analysis, predominantly low doses of thioridazine, chlorpromazine and quetiapine, which may have been used for non-psychotic disorders but rather for their tranquillising properties for non-diagnosis-specific symptoms such as insomnia and agitation; however, dose titration and augmentation should be considered – e.g. mixed therapy to control Aripiprazole induced dysregulation of prolactin levels.

Additionally, prescribing data for Wales is only recorded in DDD beginning with 2001 and prescribing data for England is only retained for 5 years (no data is available for periods before 2006). Therefore, the source data is incomplete, which had an impact on the analysis. Data is limited to GP prescribing, therefore no information is available on hospital /community prescribing (includes all FP10 prescribing apart from items prescribed by

hospitals which have been dispensed in the community – albeit quantitatively this may have been insignificant).

Furthermore, the aggregated analysis cannot account for variation between centers, identified as a significant factor in a previous study which found that units with less patients have higher rates of polypharmacy and implied therefore that clinical experience has a link to adherence to guidelines (Gören et al., 2013)

A potential direct source of information on the uptake became available at a later date (after 2014). The NICE ERNIE (Evaluation and Review of NICE Implementation Evidence) database encapsulates information collected on the uptake of NICE guidance, such as National Clinical Audit of Psychosis and Early Intervention in Psychosis Audit (Royal College of Psychiatrists), Quality and Outcomes Framework (Health and Social Care Information Centre) as well as published literature (such as large scale surveys) – and provides data on the uptake on 71 data points for CG 178 and a further 39 data points for QS80 (the Quality Standard: Psychosis and schizophrenia in adults, 2015)

The data supports the general trends of the findings from the literature review and the Prescription Cost Analysis, in relation to the gap in uptake of guideline recommendation. For example, in relation to recommendation 1.3.6.10 " 1.5.7.2 "Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment" the Royal College of Psychiatrists (2014) Early Intervention in Psychosis Audit determined that only 36 % of people with a first episode psychosis who did not have an adequate response to a full trial of two antipsychotic drugs were prescribed clozapine - and the National Clinical Audit of Psychosis (2017) found that 53% of adults with a diagnosis of schizophrenia (and not in remission) were not on clozapine, and only 21% of patients were prescribed clozapine as a single anti-psychotic.

In relation to recommendation: 1.3.5.1 (GC82 (2009); amended in CG178 (2014) *"The choice of antipsychotic medication should be made by the service user and healthcare professional together […] and discuss the likely benefits and possible side effects of each drug, including: - metabolic (including weight gain and diabetes) - extrapyramidal (including akathisia, dyskinesia and dystonia) - cardiovascular (including prolonging the QT interval) - hormonal (including increasing plasma prolactin) - other (including unpleasant subjective experiences)",* a study found that whilst 65% of NHS Trusts routinely documented how decision was made and whether this was based on a discussion with the patient, only 50% discussed weight gain side effects when deciding on antipsychotic treatment and 30% discussed diabetes and metabolic side effects - and conclude that not only this has an impact on the choice of antipsychotic but results in a missed opportunity to improve the physical health of patients with schizophrenia. (Swaby et al., 2017)

Worryingly, the National Clinical Audit of Psychosis (2017) found that 66% of adults with a diagnosis of schizophrenia were prescribed an antipsychotic above the BNF maximum (recommendation 1.3.6.3 "Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial").

As research evidence and guidelines mandate that clinicians should individualise treatment by weighing efficacy and side-effect profile of the drug with individual patient risk factors. (Lieberman et al., 2005), the question that remains is what are the factors influencing how individual prescribers achieve this balance between clinical efficacy and the side-effect risks for individual patients.

Linden et al. acknowledged that multiple clinician and patient factors combine, and they developed a questionnaire to identify reasons for switching patients to olanzapine without addressing the metabolic risks. The survey found that patient factors considered were the

severity of illness, presence of EPS and issues surrounding compliance. Clinician factors revolved around the clinical properties of the drug (specifically an expectation of improved efficacy and tolerability over the patient's current medication), their own clinical experience in respect of the particulars of the patient's condition (Linden, Pyrkosch, Dittmann, & Czekalla, 2005), and quite possible the training they may have received, as the age of the prescriber was also identified as a significant factor, with older clinicians more likely to prescribe typical antipsychotics where patient variables did not influence the choice (Hamann, Langer, Leucht, Busch, & Kissling, 2004).

In the context of EBM, as discussed in the previous chapter, there are four types of evidence that contribute to clinical decision making: research, clinical experience, patient experience and local information (Rycroft-Malone, Seers, et al., 2004). A few studies examined predictors influencing patterns of prescribing, i.e. which of the above has a preponderant influence and in what circumstances.

From patient factors, age and secondary diagnosis have been identified as predictors for atypical antipsychotic prescribing (Hoblyn et al., 2006) whilst cardiovascular and metabolic risk factors (such as baseline BMI, blood pressure, fasting glucose) did not independently predict the choice of antipsychotic (Campbell et al., 2011). King & Knapp (2006) note that older patients are more unlikely to be prescribed an atypical, whilst patients who had an episode requiring hospitalisation will be 1.5 times more likely to receive an atypical. This association with age is interesting as none of the guidelines specify age as a criteria when determining the choice of treatment, and is more likely related to risk of cardiovascular events and stroke.

Clinician factors predictive of a specific choice encompass the clinician's own perception of efficacy and predicted symptom control, and their perception of metabolic risk. Interestingly,

the perceived symptom control was lower when patients were prescribed antipsychotics with perceived lower metabolic risk, such as ziprasidone/aripiprazole (Campbell et al., 2011). This is consistent with the results of an earlier study which also notes the importance of perceptions of efficacy of alternative treatment choices (Weiden, Young, & Buckley, 2006), and with a survey of prescribing practice identified that clinicians are *'moderately'* concerned about side-effects, lack of longitudinal evidence and non-adherence risk (Correll et al., 2011)

If the perceived effectiveness of the treatment is an important determinant of the prescribing behaviour, then how is this perception formed? As the prescribing behaviour does not reflect the real data on efficacy and effectiveness, not its synthesis in guidelines, it must be that perception is formed by the clinician's own understanding / interpretation of research evidence and it relies on clinical expertise to integrate patient factors. This can only mean one of two things: either knowledge adoption is hampered (which we know can happen from theories of diffusion of innovation and adoption process (Rogers, 2003) or the *effectiveness* of a treatment does not carry the same meaning for clinicians as clinical *efficacy* from research evidence. The next chapter presents data from a qualitative study exploring the relationship between factors involved in the clinical decision-making in relation to antipsychotic prescribing.

CHAPTER III.

A Thematic Analysis of factors contributing to clinical Decision Making in the treatment of Schizophrenia: the TAnDeMS study.

"What are we to do with this information?" (Bebbington, 2001)

The literature review and PCA data analysis study has provided evidence that prescribing trends show no correlation between the strength of evidence and its uptake - and this would make the rise in atypical antipsychotic prescribing not concordant with the body of evidence about their comparative effectiveness for the treatment of schizophrenia.
The question that arises therefore is how much of this lack of implementation of evidence and guidelines is due to the lack of *translation of this evidence* into clinical practice. Contributing factors can be identified at the level of individual clinician and perceptions/ beliefs - stemming from years of clinical experience - on efficacy and balance of benefits and drawbacks in a particular formulation; it may be confounded by individual patients' preferences and weight attributed to the side-effects - which may make all the difference between adherence and non-adherence and therefore impacting on the perception of the efficacy of a particular drug; it may be attributable to marketing efforts of manufacturers targeted at clinicians, individual patients, patient organisations and self-help groups; it may have been generated by an organisational inertia in implementing new evidence, but also by other organisational factors such as pricing and budgetary pressures, formulary access policies, and overall long-term expenditure policies (accepting that an initial higher medication expenditure may reduce the incidence and cost of later inpatient days)

All these factors have been at the attention of implementation and knowledge translation models, looking at "*methods to promote the systematic uptake of evidence into routine practice and service delivery,* […] *to improve quality, effectiveness and efficiency."* (Eccles & Mittman, 2006). The Cooksey Review of Health Research also found that the investment made in health research fails to generate the benefits expected and identified *"key gaps"* in a) translating ideas from basic research into new products and b) the implementation of new knowledge into clinical practice. In order to close the gap between the evidence base and the clinical practice, the report called for a *"more effective translation of research into health and economic benefits"*. (Cooksey, 2006)

The aim of this study is to identify which of the above factors has a prevalence or higher impact in the rise of the atypical antipsychotics and how the interplay of the above factors have determined clinicians' beliefs and interpretation of what is evidence-based and therefore their impacts on clinical practice.

An initial 'proof-of concept' would be provided by prescribers themselves. It is important to identify which of the factors above (and perhaps some factors that have not yet been identified) are the most important players in their decision to prescribe one drug over the other.

In a personal view paper Bebbington (2001) identifies several reasons for a potential lack of knowledge utilisation and asynchrony between the 'evidence' and the prescribing behaviour for antipsychotics. The first reason mentioned is that evidence from trials does not help clinicians make decisions: the short time-span of the trial cannot identify the outcomes over the course of the treatment of a chronic condition. Albeit trials identify the new class of drugs with a "marginal" therapeutic advantage over their earlier equivalents and highlight a

"potentially" better tolerability given the reduced incidence of extra pyramidal side-effects – clinicians find it difficult to extrapolate and reconcile the short term advantages with the lack of the required period of experience with its use in which *"unsuspected disadvantages may become apparent".* Another major reason is that clinicians face a very wide range of (often conflicting) information that may or may not have "evidence" value – which in time generates idiosyncratic beliefs on what works and what they have less faith in and consider the guidelines to *"fly in the face of their prescribing experience"*

Bebbington points out that prescribing experience is based on the same bias as the trials: atypicals being compared to high doses of typicals. This prescribing behaviour is documented in the National Audit of Antipsychotic Prescribing conducted by the RCPsych which identified that one-fifth of patients have been prescribed typical antipsychotics on doses higher than the BNF limits, *"from a combination of therapeutic optimism and therapeutic caution"* in search of the optimal dose response curve. In the titration process increased doses are being prescribed to patients with insufficient symptom control, despite evidence that treatment response is not improved by increasing doses (Bollini et al., 1994) and treatment resistance is in fact a criterion for changing treatment to different agent (Meltzer, 1990) Moreover, PET studies (Farde, 1992) show that a therapeutic effect commences at 65% dopamine receptor occupancy levels, and extra pyramidal side-effects tend to occur after 80% - but doses prescribed in routine clinical practice miss the therapeutic window as they exceed the dose required for 100% of blocked receptors.

Bebbington concludes that *"changing the way older antipsychotic drugs are used might improve their effectiveness and tolerability"* and suggests that the prescribes consider carefully the properties of both typicals and atypicals and reconcile these with the *"needs and susceptibilities of individual patients"* (Bebbington, 2001).

This view seems to have endured for over a decade, as an editorial published in the BMJ highlights that *"truly new medicines"* are rare nowadays as drug development focuses mainly small advances on existing drugs. But these small advantages will only result in an improvement in patient's outcome if clinical experience is able to discern which patient is likely to benefit, at what dose and at what time (Godlee, 2012).

Bebbington's view that clinicians' prescribing behaviour is possibly not entirely guided by the guidelines and 'evidence' is supported by Healy (2001) who suggests that the clinicians' position that what works and what does not has been determined by *"clinical judgements, informed by visible factors such as return to work and feedback from patients, rather than judgements informed by clinical trial data"* (Healy, 2001) Apart from bias resulting from the methodological errors of RCTs (like choice of outcome measure and general lack of social functioning end-points), Healy identifies *"growing company outlay"* as having an influence on how clinical trials data is interpreted and applied.

Other factors may be related to the patient's own views, since the guidelines and evidence highlight the need to involve the patient into the decision-making process when considering the treatment options. Apart from considering the patient's susceptibility to a particular response or side-effect the clinician in search of a therapeutic relationship is bound to be exposed to the patient's subjective views on what constitutes an optimal treatment, the balance between symptom reduction and side-effects, the weight attributed to a particular side-effect profile of a drug.

A large number of publications have emerged highlighting the patient's views on antipsychotic treatment, from reviews that favour a particular drug to opinion papers on when and how they should be prescribed. Notably, in an opinion paper, Prior, Clements & Rowett (2001) advocate the importance of considering the user's experiences, and present the findings of a survey carried out by the National Schizophrenia Fellowship, Mind and the

Manic Depression Fellowship. The results of the survey highlight the strong views that patients have on the *"seriousness of the side effects, poor information about treatments, and denial of choice"*[i] which arguably led to a number of initiatives designed to counteract the lack of information and empower the patients participation in the decision making process. (Prior et al., 2001) the present study will therefore also aim to explore the role of patients' views play in the clinical decision-making.

Whilst the factors involved in decision-making and knowledge translation are well known and have been systematically developed into coherent translation and implementation frameworks, the relationship between factors and how this changes when the evidence changes is unknown.

The concept of "evidence-based medicine" has undergone substantial transformations from its initial coining as the practice derived from the "need to base clinical decisions (diagnosis, prognosis and therapeutics) on best possible evidence resulting from critically appraised rigorous clinical research" and "integrate clinical expertise and patient values".

The core principles of practicing Evidence-Based Medicine, the integration of research evidence with individual clinician experience and patient values have gained new substance: clinician experience and patient values are no longer subjective, individual and non-descript: they are too to be informed by 'evidence'.

Therefore the aim of the study is explore the interplay of factors such as 'research evidence', 'clinical experience', 'patient values', 'organisational issues' involved in decision making and detect changes in the decision-making process when a change in 'evidence' occurs.

A literature review of decision-making in prescribing, Bradley (1991) argued that to be able to understand prescribing behaviour one must first understand the main "underlying" factor: the decision-making processes. The literature on clinical decision-making in prescribing for

first episode schizophrenia is sparse, but parallels can be drawn with previous studies in decision-making in treatment options in other medical specialties or in general practice. A study by Dordević & Janković (2006) concludes that decision-making is a *"complex process influenced by many variables"*. Authors used five patient cases (vignettes) and a think-aloud technique to interview 53 GPs; the treatment choice factors were classified into two distinct categories: "core" which included the drug effects, side effects profile , comorbidity and concomitant medication, "contextual" relating to patient stated preferences and previous experiences, and "habitual" which included the prescribing habits (presumably resulting from clinical experience) and standard treatments constituting acceptable clinical practice. The categories in this study do not differ much from the EBM factors, but they do not relate to the principle of 'evidence'. The authors found that "core" and "contextual" factors were mentioned in approximately one-third of the cases each, whilst "habitual" factors were considered in one-tenth of all the interviews.

A study by Baiardini, Braido, Bonini, Compalati & Canonica (2009) looked at factors in decision-making that contribute to non-adherence to guidelines and concluded that some factors are to do with the guidelines themselves and with the implementation strategies, but there are some barriers which depend on the doctor's knowledge and skills, experiences, attitudes, beliefs and values. Notably, the latter influences the former: if clinician's behaviour is driven by a belief that he/she should follow the guideline and they agree with its content (i.e. display a confirmatory bias) this provides the motivation for acquiring new knowledge or updating outdated information. The authors identified that cognitive factors, such as knowledge and expectation of the extent of the benefit, are reinforced by andragogical factors: adults enjoy learning if this is practically relevant. This would explain why clinicians with a special interest in psychopharmacology will have their judgement shaped by on up-to-date information on pharmacodynamics rather than clinical guidelines. The study also

identified external factors: there is a strong social component, as decisions are influenced by interpersonal connections, and a marketing component, whereby tailored messages influence outcome. This follows the a pattern identified by an earlier study by McGettigan, Golden, Fryer, Chan, & Feely (2001) which states that the "medium is more important than the message". Doctors asked to rate the importance of information sources for prescribing 'old' and 'new' drugs, listed medical journals and the BNF as the sources on which they relied to gain information on both old and new drugs; in practice however, the information on the last new drug prescribed was derived mostly from colleagues and pharmaceutical representatives and MDT meetings. The study highlighted the importance of the social context, and the overwhelming influence of interpersonal relationships in the transfer of information.

An additional example of social factors influencing decision-making would be the extent to which the patient participates in the prescribing decision. In a qualitative study of 'shared decision-making' in prescribing antipsychotics (Shepherd, Shorthouse, & Gask, 2014). participants supported shared decision-making as it is supporting patient autonomy and empowering choice as well as contributing to better treatment compliance.

This finding is very much in accordance to a previously published study by Cockburn & Pit, (1997) which shows that contextual aspects (such as patient preferences) figure most prominently in the prescribing decision-making.

Some studies propose that the multitude of contextual factors influence decision-making beyond the EBM model and in fact, 'research evidence' does not play a major role (Mamdani, Ching, Golden, Melo, & Menzefricke, 2008) or they are based more on a trial-and-error methods (as progenitors of clinical experience) than objective evidence (Connolly & Taylor, 2014; Lally & MacCabe, 2015). To close the circle, Greenhalgh (2014) clarifies that clinicians' attitudes, perceptions and beliefs are crucial factors influencing application of

knowledge to clinical practice and shows that the application of evidence as defined by EBM becomes restrictive in this context.

The studies above served as a validation for this study's objectives: firstly to detect the integration of different types of evidence at the point of decision making (how do these factors interact) and secondly to explore the role of contextual influences (such as a change in guideline/evidence).

Methodology

The choice of research methodology for this study has been determined by the topic (the research questions) and the constructionist /contextualist theoretical model to which it intends to circumscribe. This is an exploratory research study, a fact-finding inquiry; this type of descriptive research has been referred to as 'ex post facto research' as the researcher reports on the state of facts and explore causes without being able to control the variables (Young & Schmid, 1966)

Holstein & Gubrium (2008) propose that a constructionist paradigm may be best suited for a qualitative enquiry aiming to determine "how social realities are produced", given that, by contrast, a naturalist paradigm overlooks 'how' people create 'meaning'.

A constructionist theoretical model stipulates that *"facts […] are socially constructed in particular contexts"* (Silverman, 2013, p.107), and this would be the logical choice to support a qualitative inquiry into how the clinical decision is reached, as a 'construct' based on the 'context' as perceived by the actors; from this perspective the contributing factors proposed by EBM models (research evidence, clinical expertise, patient values) become the context , as variables outside the control of the researcher.

Several models of qualitative enquiries share the constructionist theoretical proposition, such as grounded theory, narrative analysis and discourse analysis.

Miles, Michael, & Saldana (2014) propose that the method of choice is conditional upon the level of "prior instrumentation": a 'no prior instrumentation' assumption means that the fieldwork must be left open to surface phenomena that may have been concealed or confounded by the instruments of previous investigations; an 'open question' on the other hand, assumes that within a small sample, a cross-case comparison is of limited value, and therefore there is no utility in identifying rigid standardised research instruments.

In view of the above, a constructionist model is appropriate as the study aims to identify how factors interact; within a qualitative methodology, Thematic Analysis is best suited to a hypothesis generating type of enquiry.

Thematic analysis has been defined as a method for eliciting patterns (themes) in the qualitative data, and is an *"accessible and theoretically flexible approach"* (Braun & Clarke, 2006 p.78) and therefore compatible with the constructionist paradigm.

Other methods, such as Grounded Theory or Interpretative Phenomenological Analysis, which also seek pattern in the data would not have been suitable in this instance as they are theoretically constrained, either in epistemology or in theory development (Holloway & Todres, 2003; Smith, 2008)

A distinct advantage is that, unlike other methods that passively discover 'themes that emerged' and concepts 'imbedded in the interviews' (Rubin & Rubin, 1995, p.226), thematic analysis can actively search for the theme that are of interest. In keeping with a constructionist/contextualist paradigm we know that meaning and experience are socially produced (Burr, 1995) so thematic analysis can look at ways in which experiences are created by the social context, ways in which individuals create 'meaning' from their experience and this meaning is shaped by the social context – and can therefore *"unpick or unravel the*

surface of reality" (Braun & Clarke, 2006, p.81). From a pragmatic point of view, the utility of thematic analysis as a method is that it has flexibility and can condense key features of a large data-set, can easily identify the prevalence of a particular theme by looking at similarities, connections and variances across data, and, most importantly, allows for unanticipated insights by not using an *a priori* coding framework – described as an inductive approach. This is an essential trait for a hypothesis generating study, particularly in this context, where the aim is to explore the dataset for the prevalence of factors that make up the meaning of clinical decision making, rather than look for specific factors in a hypothesis testing sort of way.

As far as the research technique is concerned, the data collection combined an observational method (within a 'think-aloud' framework) with a semi-structured interview. The observation has the advantage that that it allows to understand what happens (i.e. the behaviour) during the decision-making process, without the confounding factors induced by 'prior instrumentation'; the semi-structured interview allows to determine 'experience' and 'motivation', without necessarily being directive.

The 'think-aloud' method was chosen for its capacity to reduce the ethical implications, minimise the Hawthorne effect and allow for a certain degree of generalizability. Its methodological advantage resides in the simple verbalization process and it sidesteps interpretation by the subject, whilst the obvious disadvantage and challenge to any empirical approach is that is it not replicable (Van Someren, Barnard, & Sandberg, 1994, p.39)

As a method, it is useful in so far as it elicits real data on reasoning during a problem-solving task. By comparison, the alternative would be to ask participants to describe their reasoning, but this account may be incomplete or incorrect, based on a selective memory retrieval. Participants may be tempted to describe it in terms of pathways that they have been taught to undertake in clinical assessment, not necessarily accounting for the fact that in real-life

scenarios the process often deviated from such protocols. Another alternative would have been to look at decisions already made for an existing patient but this would have only elicited the product of the thought process, and not yielded information on the thought process itself. Using a real-time think-aloud method allows the researcher to understand how the participant arrives at a counclusion, what was considered, what was omitted or easily dismissed, what elements were difficult or easy to tackle, and how was conflicting information dealt with.

The aim of the interview is to derive information on the 'motivation' and 'meaning' and to clarify some of the processes involved. This approach is necessary to counteract some of the disadvantages of the think-aloud method used in isolation: Branch (2000) identified that the problem-solving exercise and concomitant speaking may be too much of a 'cognitive load' for some participant and Fonteyn, Kuipers, & Grobe (1993) found that a follow-up interview provided valuable information and made the data resulting from the think-aloud exercise easier to interpret. Using this method would adequately ensure that themes emerging will be analysed as an integral part of a larger concept: connections can be analysed as clusters of larger categories rather than individual entities, i.e. it would enable to analyse the factors identified by clinicians during the decision-making process, not insolation but in relation to one another. This is supported by the view that research, clinical experience, patient and carer experience, and information on local context and environment are melding sources of evidence (Rycroft-Malone, Seers, Titchen et al., 2004) in the delivery of care.

Sample

Potential participants were recruited from a large Health Board (NHS Trust) in Wales, and the only inclusion criteria was experience in prescribing for schizophrenia. All clinical grades and nurse prescribers were eligible to take part. The study received ethical approval from

Bangor University, School of Medical Sciences Academic Ethics Committee and was granted research governance approval from the R&D Committee at the Health Board. No NHS REC ethical approval was required as the study fell outside the requirements of the Governance Arrangements for Research Ethics Committees, by recruiting NHS staff as participants.

Whist this sample is not necessarily representative of the target population it can be considered an adequate sample for a hypothesis generating qualitative study; given the range of clinical expertise and the diversity of the 'context' at the three hospital sites of the organisation, the heterogeneity of the sample should be an advantage. Whist in quantitative research the sample needs to be sufficiently large to accommodate the demographic characteristics of the population studied and to identify a specific effect size, in qualitative research the number of participants in a study is less important than the depth and quality of data derived from this sample. Thematic analysis (as a precursor of grounded theory) uses a 'theoretical sampling' to identify the properties of a 'category' and to develop comparisons of settings which may modify or broaden this initial category. Bryant & Charmaz (2007) advocate that theoretical sampling requires acquiring new data to until the properties of a theoretical category is saturated (p292). From this perspective no more data (i.e. participants) will be required once saturation is reached and no new themes emerge, and Guest, Bunce, & Johnson (2006) also support the idea that a purposive sample size should be determined by saturation, but admit that it is difficult to ascertain how large the sample ought to be for saturation is reached as there is no "test for adequacy"; in addition, not only data saturation is driving the sampling process: in a non-probabilistic, purposive sampling, participants need to be selected according to the criteria relevant to the research objective (i.e. psychiatrists who have experience of patients with schizophrenia) and take into account heterogeneity.

Based on the above, the following principles were followed for sampling in this study: the selection followed a theoretical framework (thematic analysis), participants have been chosen

purposefully for their experience in the area and aiming for a heterogeneity, and the sampling was sequential, to allow for saturation to develop. An a priori sample estimate for this study was of twelve to twenty participants, with the proviso that this was a theoretical sampling and data collection will stop once either the principle of heterogeneity was no longer satisfied, or data saturation was achieved. This sampling method was also consistent with the complex nature of the think-aloud task: this seeks rich in-depth data from individuals, rather than population-wide generalisable data, but the synthesis allows comparisons to be made across subjects and therefore some inference can be made about the reasoning process of a group with similar expertise (Kuipers, Moskowitz, & Kassirer, 1988).

The final sample included 14 participants, out of which three senior consultant psychiatrists with over 20 years' experience at consultant level, four mid-career consultants, with 5 to 10 years' experience at consultant level and two recent appointment with less than 3 years' experience at consultant level – and three training grade psychiatrists (Specialty Trainees formerly known as Senior House Officers and Specialist Registrars) and two RMN nurse prescribers of seniority level, with over 10 year's experience – and 11 transcripts were used in the final analysis.

Data collection and analysis

Participants who consented to take part in the study were asked to carry out a think-aloud exercise in the context of a semi-structured interview.

All eligible staff received and email alert regarding the study and potential participants who expressed an interest were sent further details about the study (the Participant Information Sheet, Appendix A) and an interview dare/time was arranged. Written informed consent was sought on the day of the interview (Appendix B).

The think-aloud exercise required participants to verbalise the thinking process during the clinical-decision making for a hypothetical patient with first episode psychosis presented in a vignette. The think-aloud method followed a standard protocol as described by Fonteyn, Kuipers, & Grobe (1993). The method requires 'simulation', and it involves the presenting the subject with a written case study to provide some of the elements of the case, whilst controlling for other variables by providing further information in segments. In this study, participants were presented with two 'vignettes' representing the clinical scenario of a hypothetical text-book case/patient with a first episode schizophrenia and asked to 'think-aloud' his/her clinical decision-making process in the assessment of this 'patient'. The think-aloud method was explained and examples were given to ensure all participants understood what is required and to ensure consistency between participants. The vignettes were drawn by considering the elements required for the diagnosis of schizophrenia, with sufficient details to mimic a real case but with a 'lack of specificity' to enable eliciting a differential diagnosis, and equally with a paucity of details that would elicit further information seeking behaviour. The vignettes (Appendix C) were constructed under the supervision of my academic supervisor and independently verified for validity by two other consultant psychiatrists who were not part of the study. Observing a think-aloud' exercise of a vignette instead of observing a real-life consultation has also the advantage of minimal intrusion: it is very unlikely that a patient would agree to being observed during a consultation and if consent would be given, it is likely that a number of confounding factors, amongst which the presence of the observer, would denaturate the observation; presenting the same vignettes to all participants allows for comparative inference and allows to derive common themes mentioned by all participants.

In keeping with the think-aloud standard protocol, study participants were asked to agree to a dedicated time, when the think-aloud and interview could be conducted undisturbed, in privacy. Assurance was sought that the participant understood the scope of the study and methods to be used. The think-aloud exercise and the subsequent semi-structured interview were audio-recorded. Participants were presented with the vignettes and asked to think-aloud as they problem-solved the clinical scenario and were reminded to keep thinking aloud if any pauses occurred which were indicative that they are not verbalising the thought process – but otherwise interaction was kept at a minimum, to avoid leading or influencing the direction of the thought process. Written notes were made to keep an account of things that were not captured by the audio-recording: body language, flow of thoughts, points that require further clarification. The notes became part of the iterative part of the analysis.

The semi-structured interview sought clarifications on points raised during the think-aloud exercise but was otherwise unguided and participants elaborated freely on the diagnostic, differential diagnosis, potential therapeutic pathways, concerns, etc.

The recordings were transcribed verbatim using a standardised transcription protocol (McLellan, MacQueen, & Neidig, 2003) preserving morphologic naturalness, including mispronunciations, non-verbal sounds, hesitations, in brief anything that may help understand the context in which things were said – but ensuring that all data was fully anonymised. No participant identifiable information (such as name) was recorded, but details that may have helped identify a participant (such as hospital, or location) were removed or changed to a study specific identifier (e.g. hospital x, or ward z). Transcripts were later moderated for accuracy by a research assistant independent of the study, and the final version of each interview was sent to individual participants, so that they can verify the veracity of the data and ensure that the interpretation was correct. At this stage, two participants requested to

withdraw from the study: one participant had concerns that what was said during the interview may reflect unfavourably on his clinical practice, the other participants felt that their clinical decision-making may be judged as lacking in some way, as the interview had not captured well the totality of a patient's journey. Those interviews were removed from the dataset and further efforts were made to reduce any items with potential ethical implications. For example, to prevent any judgement calls on the appropriateness of prescribing in relation to the patient presentation, the name of the drug was removed from the transcript and replaced with [typical] or [atypical] so that no direct link could be made back to individual prescriber, based on their actual prescribing preferences.

Braun & Clarke, (2006) describe a set of decisions that have to be made about how data will be analysed, depending on the aim of the study. Inductive analysis could be used if the intent is to have data-driven themes, i.e. coding the data without a pre-designed coding framework or set category of codes. Conversely, a deductive, or theoretical analysis is driven by a specific analytic interest, a specific research question and codes are designed beforehand to look for content in the discourse that map onto that specific feature. As the purpose of this study was exploratory, an inductive analysis method was used, to allow the data to 'speak' about the factors that are considered in the decision-making process. It must be said however that even an inductive analysis does not happen in a theoretical vacuum, and given the findings in the literature and the principles of EBM there were some determinants on how things may get coded in relation to clinician experience, patient factors, research evidence, etc.

Additionally, Boyatzis (1998) describes that thematic analysis has a choice in identifying themes, either at semantic/explicit level, or at a latent/interpretative level: at a semantic level, themes are identified by considering only the surface meaning of what was said (in a way

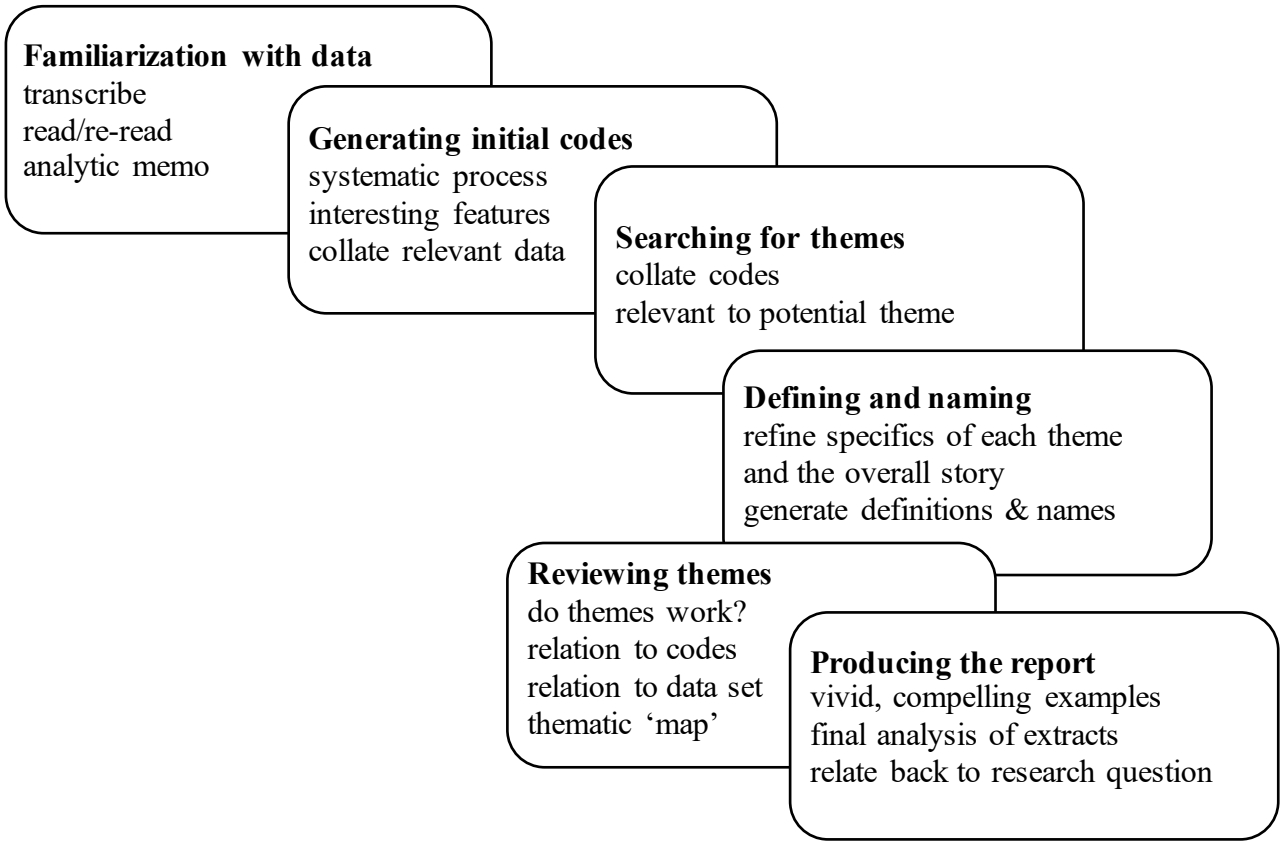
taking things at face value) and Patton (1990) explains that the analysis involves a description of data organised in way that illustrates the patterns, and can be subsequently examined to understand the significance, meaning and implications of these patterns. Alternatively, the latent level looks at the meaning of what was said, at the underlying ideas and assumptions that presumably informed the subject's expressed views (i.e. the data). For the purpose of this study a semantic level was chosen, as the latent level was felt to be too speculative and open to interpretation bias. In order to examine the meaning and significance of patterns the semantic codes derived initially were looked at in keeping with the 'vocabulary of concepts' in the standard think-aloud protocol - adapted from Fonteyn et al. (1993, p.436). The codes were defined as: Action = the action taken, the manner of acting; Sign = objective clinical information considered; Time = a chronological reference, sequence of event; Treatment = therapeutic solution, pharmacological / psychological intervention choice; and Value = rating/scale of usefulness or importance/worth of information. These were analysed as to whether they are Connotative (denoting meaning), Indicative (denoting significance) or Causal (denoting cause and effect relationship) as described by Fonteyn et al. (1993, p.437)

In practical terms the analysis followed the 6 phases of thematic analysis as described in Braun & Clarke (2006) (Figure 13).

Part of the familiarisation process, after transcribing was to read and re-read the data and sketch an analytic memo for each interview, as an initial assumption about possible connections between categories and/or their respective properties. This was an instrumental construct as it allowed a 'free-from' categorisation, an inference about the semantic meaning of the data and an initial assessment of potential factors that were mentioned in each interview.

Figure 13.

Phases of Thematic Analysis



Source: based on Braun, V. & Clarke, V. (2006). *Using thematic analysis in psychology,* Qualitative Research in Psychology, 3 (2) pp77–101. ISSN 1478-0887. p 87 © Taylor & Francis (2006) CC BY-NC

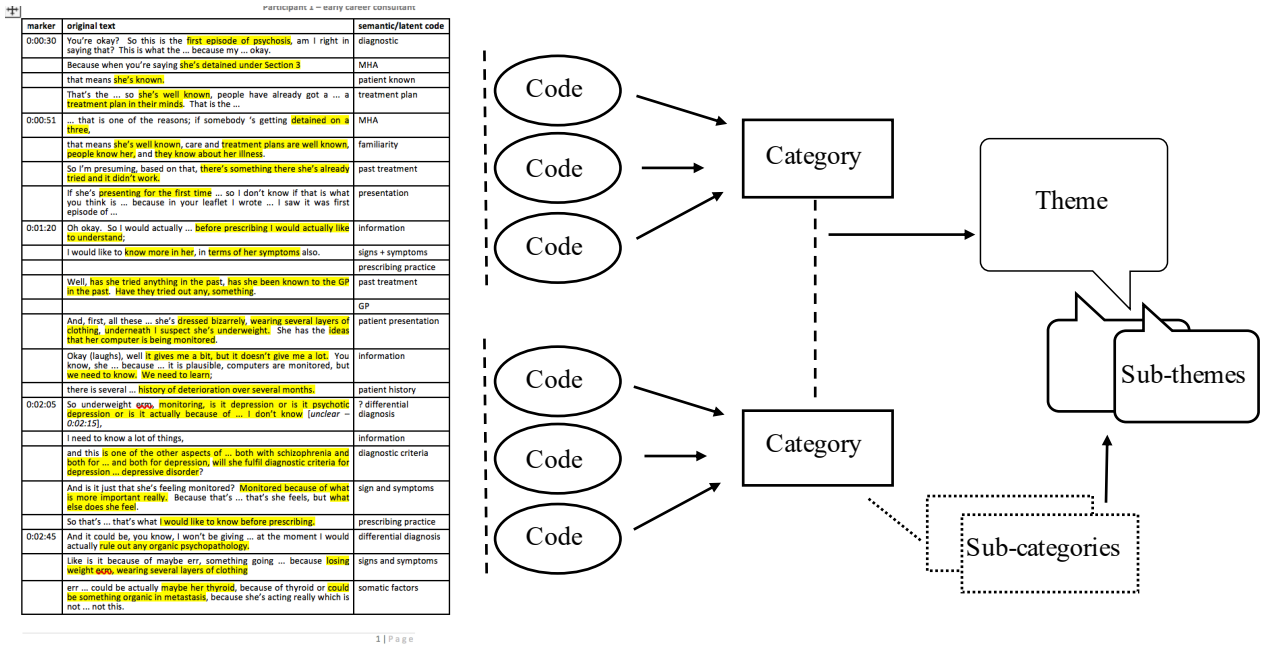
The second phase involved generating initial codes and collating relevant data. For the purpose of this study, coding was done manually, rather than using software, as a learning experience, using as a guide the Saldaña (2014) coding manual. A code is described in the manual as a *"word or short phrase that symbolically assigns a summative, salient, essence-capturing, and/or evocative attribute for a portion of […] data."* The mechanics of coding were quite straightforward, albeit the description appears to be complex: the printed transcribed text was separated in short paragraphs which were part of the same semantic context, and words or short phrases were highlighted as a pre-coding memory aid (a

technique described as ‘pawing’ by some authors). The text yielded a great number of potential codes and to correct this, and in keeping with the coding manual, the text was re-coded for patterns, and subsequently ascribed to categories, which then were used to build a ‘code-list/thematic map’ that summarised the main concepts that appeared in each category. For example the ‘Risk’ category, contained codes such as ‘risk to self and others’, ‘risk from medication’ risk of recurrence’, risk is worthwhile’; similarly, for example, the category labelled ‘Side-effects’ contained all codes relating to it, either mentioned as a factor that the clinician would consider in decision making, or mentioned as a tolerability factor that should be explored with patients (Appendix D). These categories were a very useful starting point for the third phase, i.e. collating codes and searching for themes. A ‘cut and sort’ technique was used to assemble the information. Where a paragraph could have been ascribed to two or more codes this was duplicated as a ‘co-occurrence’. For example, a paragraph mentioning ‘side-effects’ could indicate either a mention in relation to the treatment decision, or that the clinician had considered this to be a trade-off with efficacy – in which case it was coded under both codes. Each code and its respective context was cut from the transcript and similar codes were pasted on a larger sheet labelled with the name of the category in the code-list (Appendix E). The source of the code was identified by colour (each participant’s transcript was ‘pawed’ using a different colour highlighter) and the time-frame (a note to identify where it appeared in the interview transcript).

The next phase was to examine the code-list sheets and refine the specifics for each of the potential themes. Items that formed categories of repeated patterns, similarities, indigenous typologies, analogies (and differences), and linguistic connectors made up the themes. Some sub-themes were identified where this served the purpose either analysing discrepancies or exploring inferential, connotative or causal relationships (Figure 14). Themes were then named/defined by the ‘story’ they told.

Figure 14.

The "Codes to Themes" model for qualitative enquiry



Participant 1 – early career consultant

marker	original text	semantic/latent code
0:00:30	You're okay? So this is the first episode of psychosis, am I right in saying that? This is what the ... because my ... okay.	diagnostic
	Because when you're saying she's detained under Section 3	MHA
	that means she's known.	patient known
	That's the ... so she's well known, people have already got a ... a treatment plan in their minds. That is the ...	treatment plan
0:00:51	... that is one of the reasons; if somebody 's getting detained on a three,	MHA
	that means she's well known, care and treatment plans are well known, people know her, and they know about her illness.	familiarity
	So I'm presuming, based on that, there's something there she's already tried and it didn't work.	past treatment
	If she's presenting for the first time ... so I don't know if that is what you think is ... because in your leaflet I wrote ... I saw it was first episode of ...	presentation
0:01:20	Oh okay. So I would actually ... before prescribing I would actually like to understand;	information
	I would like to know more in her, in terms of her symptoms also.	signs + symptoms
		prescribing practice
	Well, has she tried anything in the past, has she been known to the GP in the past. Have they tried out any, something.	past treatment
		GP
	And, first, all these ... she's dressed bizarrely, wearing several layers of clothing, underneath I suspect she's underweight. She has the ideas that her computer is being monitored.	patient presentation
	Okay (laughs), well it gives me a bit, but it doesn't give me a lot. You know, she ... because ... It is plausible, computers are monitored, but we need to know. We need to learn;	information
	there is several ... history of deterioration over several months.	patient history
0:02:05	So underweight ecto, monitoring, is it depression or is it psychotic depression or is it actually because of ... I don't know [*unclear – 0:02:15*],	? differential diagnosis
	I need to know a lot of things,	information
	and this is one of the other aspects of ... both with schizophrenia and both for ... and both for depression, will she fulfil diagnostic criteria for depression ... depressive disorder?	diagnostic criteria
	And is it just that she's feeling monitored? Monitored because of what is more important really. Because that's ... that's she feels, but what else does she feel.	sign and symptoms
	So that's ... that's what I would like to know before prescribing.	prescribing practice
0:02:45	And it could be, you know, I won't be giving ... at the moment I would actually rule out any organic psychopathology.	differential diagnosis
	Like is it because of maybe err, something going ... because losing weight ecto, wearing several layers of clothing	signs and symptoms
	err ... could be actually maybe her thyroid, because of thyroid or could be something organic in metastasis, because she's acting really which is not ... not this.	somatic factors

1 | Page

Source: based on Saldaña, J. (2014). *The Coding Manual for Qualitative Researchers*. *Sage*. https://doi.org/10.1007/s13398-014-0173-7.2 (Figure 1.1 A streamlined codes-to-theory model for qualitative inquiry, p. 12) @Sage (2014) – with permission

A fifth phase of the analysis involved further refining of the themes, by looking back at how they mapped on the original analytic memo, to the interim code-list/thematic map and essentially to the raw data in each interview. Some themes required re-naming to better reflect the content or the context of the data.

Finally, the report was produced, as presented in the Results section below.

Results

The study generated six themes salient to the research question and relevant to the factors described in initial literature review in relation to clinical decision-making in prescribing for schizophrenia.

Themes that are related to clinician specific (own) factors have cognitive and emotional contributors. They rely on their own clinical experience, and on the tried and tested opinions of others, more often than on 'research evidence' or 'guidelines'; their approach varies based on the education and training they had, but mostly on their values and beliefs they hold on treatment options, on their own abilities and on the influence of others.

Themes related to patient factors revolve mainly around risk assessment and risk management, and collaboration with patient in decision-making is seen either as a means of reducing risk of non-compliance or as means of ensuring that side-effects are not becoming a risk.

Theme 1 Ownership, collaboration and modelling

As clinical work is often carried out in a multidisciplinary team, clinicians tend to model their behaviour based on group influencers. The extent to which they lead the decision-making in the group, collaborate with colleagues, rely on colleagues for decision-making or are influenced by colleagues' opinions depends on experience, role in the team, and individual values and beliefs. This is not a novel observation, but it has generated a new insight: these are not mutually exclusive categories (i.e. extensive experience does not always equate to a need to lead the decision-making process) and the role of behaviour modelling is to bridge the knowledge gap between the clinician's interpretation of research evidence and its practical clinical application. In addition, it seems that the level of responsibility accepted depends on what aspect of care is being discussed.

Sub-theme 1: Eminence-based medicine is alive and well

Clinicians with limited experience or limited self-assurance identified a senior colleague as the primary source of information for their decision making or as a 'validator':

> *"all the stuff I said about antipsychotics, it comes from the discussions with the Professor."* [foundation year doctor]

> *"Yeah, the consultants do* [prescribe this], *and then people have responded, when we're down the line* […] *you read ... you will be taught, so that's how it is."* [foundation year doctor].

> *"*[…] *as a nurse prescriber, this would be something I would certainly go through* […] *a consultant with."* [nurse prescriber].

> *"essentially, I've just observed other consultants prescribing*" [foundation year doctor]

> *'I can't remember if I heard it correctly,* […] *I don't know if I've made that up and it's just complete rubbish* […] *I'd have to check with my consultant"* [foundation year doctor]

> *"The other thing I do is …erm… the hospital will have a pharmacist who will be checking medications and prescriptions every day* [...] *and then the pharmacist comes in and would be very happy to discuss."* [mid-career consultant]

> *"it's a drug that some of the staff figure is too gentle as it were ... they are not absolutely convinced that it works"* [senior consultant]

Clinicians who rely less on colleagues are happy to put forward their own point of view; they often do this as if they were teaching or exemplifying, using second person singular in a directive sort of way:

> *"some of my colleagues might say, you know, put them on* [proprietary drug brand name(typical)] *but I say …you may be …err, better symptomatically but you have other problems"* [mid-career consultant]

> *"then I would probably give a trial of a neuroleptic, such as* [proprietary brand name(atypical)] *because I'd be uncertain about compliance.* [proprietary brand name(atypical)] *it's quick to hit things, so you'd know that someone was taking it* […] *partly the efficacy would relate to their compliance, so you'd want to kno*w" [senior consultant]

> *"depot takes four half-lives to get into your system, it's a very slow way of doing things, you wouldn't want to introduce a depot at this stage"* [senior consultant]

> *"….so the ones you're meant to offer it to… I think it' about thirty-nine percent with treatment resistance… that you can consider it"* [mid-career consultant]

> *"my choices are driven primarily by what I want to achieve in the short-term: so if you give* [proprietary brand name (atypical)] *they are very sedated, but if you give* [proprietary brand name (atypical)] *they are probably very excited … or not excited by it does not give any sedation… so you can give* [proprietary brand name (atypical)] *instead."* [senior consultant]

Participants shifted responsibility onto other members of the team more often when talking about research evidence.

> *"I have a colleague next door to me who actually gives us lots of information on the best drugs*" [senior consultant]

> "*They have done trials with a lot of antipsychotics…it's the commissioners and things like that, they say there is not a lot of evidence"* [early-career consultant]

> *"I think people who have seen more… they have gone from typical to atypical and back to typical"* [mid-career consultant]

> *"…so some journal club will come up and somebody will talk about drugs* […] *you are not just relying on one journal or article, you have the opinion of peers"* [mid-career consultant]

> *"we have a colleague* […] *he is interested in researches on medication. He will circulate only stuff that he thinks it's worth circulating"* [mid-career consultant]

The use of the third person plural in this context suggests the participant did not feel responsible for assessing and applying research evidence to their clinical practice, whilst the reference to deriving evidence from colleagues signifies reliance on a senior or more influential member of the team to provide this evidence, rather than being self-sufficient in acquiring that information.

Sub-theme 2: Various degrees of responsibility for different aspects of care

Participants took varying levels of responsibility for parts of the patient management process depending on the aspect of care they were discussing. Some took full responsibility for the care of the patient - indicated by use of the first person singular: participants consistently use *'I'* when gathering information and forming a diagnosis. They also take ownership of the risks associated with prescribing – but this does not seem associated with experience.

> *"So now I can change the* [proprietary brand name (atypical)]*, but I can't change the diabetes"* [early-career consultant].
>
> *"before prescribing I would actually like to understand* […] *I would rule out any organic psychopathology* […] *I would not actually prescribe anything, I would do the physical examination first"* [foundation year doctor].
>
> *"I would like to just give her something to calm down"* [mid-career consultant]
>
> *"I might use low dose neuroleptics as non-addictive tranquilisers if the patient is particularly distressed"* [senior consultant]

Other participants indicated they would share responsibility of patient care, particularly for risk management - as indicated by using the first person plural. For example, when discussing risk management, one mid-career consultant repeatedly states "*we need to manage".* Another participant [nurse prescriber] uses "*I"* when planning the assessment and their immediate plan, however they use "*we*" when discussing antipsychotic prescribing. Some participants recognise the importance of working with colleagues to reach a diagnosis in borderline cases. This could match the uncertainty that they feel with prescribing; in comparison to the other participants they are slow to recommend antipsychotic prescribing.

> *"One of the things you gain by people being in hospital is you get the chance for a few different people to see them err, over a period of a few days, and that can be tremendously useful."* [senior consultant].

Some participants, in particular mid-career consultants, indicated they would use other healthcare professionals to help gather information saying, "*you might get some information from the GP*" and *"let the nursing staff observe".* However, when taking about the treatment plan, they said, *'then you decide"* which suggests they were ultimately the one to make the decision about treatment, but at subconscious level they may dissociate from this by using second person singular to exemplify. This shift from first to second person occurs also in the context of didacticism, as discussed in the sub-theme above, and is common to participants who felt their experience is often called upon by colleagues.

Sub-theme 3: Normative values and beliefs shape the actions

Participants refer to their clinical experience in many ways: some participants place greater emphasis on clinical experience and frequently use the experience with previous patients to guide their clinical decisions - but do not seem to recognise that it is the factor with greatest impact; others appear to have less confidence in their own clinical experience and place emphasis on their 'social position' to defer to the judgment of others. This theme questions how this disparity impacts prescribing.

For participants who justify treatment by referring to their clinical experience, their beliefs regarding treatment and assessment appear to be based on their experience with previous patients.

> *"I've had patients who err ... presented with anorexia and I was treating them, and then they started to develop psychosis"* [mid-career consultant]

> *"You know, why are we saying suicide risk? say is it the patients is depressed the drive for suicide risk is different, I'm hopeless, I'm helpless, not future, whereas I've had patients who are suicidal because the want to escape from persecution"* [mid-career consultant]

> *"…because I know otherwise they'll have long term complications .. you know, like I had a patient recently who I saw for twenty years had developed tardive dyskinesia…"* [mid-career consultant]

> *"it depends: I have patients who are on* [proprietary drug name (atypical)] *30 mg, or on* [proprietary drug name (atypical)] *500 mg who are slim and they are doing very well"* [senior consultant]

> *"… because I had a patient many years back, he was involved in drug taking and… meeting some prostitutes…every time he sees a CCTV he is worried he is being followed… and this is how shame becomes a projection unto somebody else, so obviously I think the psychodynamics of patient's experience is very important"* [senior consultant]

Clinicians who are hesitant about they position in the group tend to doubt their clinical experience and will rely on others to reach a decision:

> *"… it would be very, very.. err, unwise I think to go against erm ... what erm, seems to be erm, the evidence base norm amongst experienced psychiatrists that I work with certainly."* [nurse prescriber]

> *"oh… you'd discuss the pros and cons…"* [foundation year doctor]
>
> *"the key thing is when you give a poison to a person you have the nursing staff all around the ward really engaged with looking at well.. is there a difference"* [senior consultant]
>
> *"I'd want to get a key worker to see him a few times* […] *get a chance for a few different people to see them…"* [mid-career consultant]
>
> *"I'll look at the joint formulary* […] *I'll seek advice from the pharmacy and the team…and the family really around the prescribing, because they will have to monitor that'* [early career consultant]
>
> *"For me, because I am working with two different consultants and they have very different ways of prescribing* […] *and I have to take that into account"* [nurse prescriber]
>
> *"I think it would need a multidisciplinary approach really to deciding erm ... and erm, ... agreeing"* [nurse prescriber]

Theme 2: The value attached to information is contingent on its source

This theme supported the information-processing model of decision-making, which revolves mainly around the way complex information is managed. The study showed this to be a linear process: whilst participants rely on others to generate the information they require to be able to make a decision or fill in the gaps, the resultant information is weighed, and the source of the information plays a major role in establishing its validity and its value. Moreover, there is a link between the type of information and how it is gained, as well as between the sources of the information and the end-purpose it serves. For example, for diagnostic purposes information is sought in relation to the clinical presentation and patient's circumstances: the information elicited from the patient is attributed limited value; information gained from colleagues, (ward staff, GP, key worker) or the patient's family appears to carry more weight.

> *"what you are lacking here is a collateral history* […] *we'd like to know a lot more about the baseline personality* […] *part of me would certainly want to ask her"* [mid-career consultant]

> *"get her seen on the ward for a period of time, for us to get a feel for just what actually is going on and what she'd look like without treatment, get to know her a bit more, maybe get to chat to the rest of the family to let us know what she's normally like"* [senior consultant]

> *"it gives me a bit but it doesn't give me a lot* […] *I need to know a lot of things* […] *will she fulfil diagnostic criteria, can I rule out organic psychopathology* […] *how does he reach a decision, if it's a consistent thing, if it's shakeable, can he undertake alternative explanations"* [early-career consultant]

> *"I'd want to get more information and the information probably … one would be family, and the second if there is a GP locally* […] *what they have observed, who brought her the hospital"* [mid-career consultant]
> *"because I'm a nurse this would be something I would certainly go through a consultant with"* [nurse prescriber]

> *"I need more history and rule out substance misuse* […] *more GP input or maybe history form relatives "[*foundation year doctor]

The value attributed to information derived from the patient changes when the topic transitions from diagnostic to treatment choices; here we see that information is sought from the patient in relation to treatment preferences, outcomes or the limits of tolerability of side-effects – and this information weighs substantially in the decision-making.

> *"once she goes on these pills she is the only one who knows what's actually happening to her and she needs to let us know whether there is anything useful happening"* [senior consultant]

> "if she is very keen in her self-image and she does not want to put on weight, I'd probably avoid medication" [senior consultant]

> *"so if she said, 'No, I don't want to gain weight, of course I'll go for* [generic drug name (atypical)] *which does not cause much weight gain.* […] *but later on they might say 'No, this is causing me side-effects'. "* [foundation year doctor]

> *"then he said 'Yeah' because I had already given him all the information, then he chose* [generic drug name (atypical)]." [mid-career consultant]

Many participants worked with the patient to inform their prescribing decisions, but the complexities of this aspect were explored in distinct theme further on.

In relation to how research evidence is utilised, peers' opinions are definitely the influential factor in how information is acquired (and this is discussed at large in the theme relating to research evidence) but that information seems to weigh more than the patient's views, with

research evidence being prioritised as the most objective and relevant source of information in planning and undertaking treatment. Participants often refer to evidence that side-effects are undesirable, or that research evidence shows that patients want efficacy; this serves then as a frame for the discussion with the patient.

> "*I would normally want to a) find out why they are fixed on that particular drug, and b) dissuade them* [...] *and go for one that has better efficacy.* [senior consultant].

> *"I would err, outline the likely side effects, but also say because we're not hitting you with a maximum dose* […] *the side effects are not likely to be severe"* [nurse prescriber].

The weight attributed to other clinician's views is justified by either experience or evidence / guidelines:

> *"it's based on years of experience of treating psychotic behaviour* […] *with the medical expertise contained on the err, prescribing course. And in books like the Maudsley and the BNF."* [nurse prescriber].

A confirmation bias appears in most interviews: sources of evidence that confirm to their own views are implicitly trusted.

> *"I know* [generic drug name (atypical)] *caused more weight gain and diabetes, but we think of like… these are a bit more safer* […] *and we've got evidence that this works, they have been proved to be having more response."* [foundation year doctor]

> *"what I know is that there are two main types of side-effects that you're worried* […] *and there is a lot of research that says that patients who put on weight are more likely to respond."* [mid-career consultant]

> *"definitely not …erm, a typical antipsychotic medication because I believe there is more side-effects in relation to that* […] *so I will look at NICE guidelines"* [nurse prescriber]

Preference for one class of drug is informed by vicariously by peers, rather than own assessment of research and guidelines, and this is discussed in the theme below.

Theme 3: Trust in research findings and guidelines is based on anecdotal validation rather than individual critical appraisal

This theme demonstrates that most clinicians rely on their peers to integrate research knowledge in their clinical experience. Referral to guidelines and research findings is not always accompanied by language that exudes confidence: whilst the awareness and understanding is apparent, the discourse is hesitant and not necessarily reflect critical appraisal terminology

Some participants are more confident and derived information from their own interpretation of research evidence and make statements of their choice of drug based on efficacy in relation to a particular aspect of the patient's presentation.

> *"I look at efficacy data for antipsychotics primarily and not just form my own study but from a lot of very good recent meta-analyses. We now have a good idea of how the different antipsychotics rank in terms of efficacy. We know how they rank in terms of side-effects as well, but in terms of efficacy the number one is* [generic drug name (atypical)]*, followed by* [generic drug name (atypical)]*, and* [generic drug name (atypical)]*, and then with a gap followed by* [generic drug name (atypical)] *and* [generic drug name (atypical)]*, and err..* [generic drug name (typical)]*, then with another gap followed by* [generic drug name (atypical)] *and* [generic drug name (atypical)]*, where the efficacy data is not very good at all. I realise that efficacy data is limited for all antipsychotics, but equally I do believe that many people get some benefit from antipsychotic medication."*[7] [senior consultant]

> *"so I think I may …I try to follow the NICE guidelines, but NICE guidelines for schizophrenia or first episode psychosis are a bit incomplete nowadays, because there has been a very good systematic review of the meta-analysis published in 2013, that is very good summary of the situation now, and errm, beneath that all antipsychotics work the same or have the same side-effect profile is gone, but it's actually not true. There is now very good evidence that some antipsychotics are better than others, full stop.* […] *so I plan to follow that indication until we have better evidence I would like to say, I tend to follow this kind of …erm… from a technical point of view.* […] *so in this patient I would probably go for* [generic drug name (atypical)] *as the first choice because it sounds more like a general psychosis and not necessarily like a particularly paranoid picture. I would also go for* [generic drug name (atypical)] *if impulsivity is a particular problem, which doesn't seem to be the case here either.*" [senior consultant]

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[7] This is an interpretation of Leucht et al., (2013) and reproduces the findings of the study with a high degree of fidelity, apart from chlorpromazine, and does take into consideration the discontinuation rate as a measure of efficacy.

Some are more hesitant or indicate that they rely on colleagues:

> *"it was because… you read in the medical school what is the latest guideline, what is the latest research, because that is what we were thought all the time, is read this research article which came out today; so we are not told to read the research article which came out in let's say 2000, if its 2006 you are doing ..working in 2006; what's the latest is what they want you to do* […] *and then the national guidance, like NICE and all, they were advocating the use of atypicals more than typicals; recently they have come back, they have still not come back, it's the commission and things they say there is still not a lot of evidence. There are big studies like CATIE and things, coming out and saying hold on, not a lot of evidence, it's more of side-effects with atypicals, you think they re very cleaner drugs, they are not!, so those things come into the picture and linked to clinical practice."* [early-career consultant]

> *"I have a colleague next door to me who actually gives us a lot of information on the best drugs, you know, lots of information. So he uses* [generic drug name (atypical)] *... which has the best… you know, in terms of response rate, etc, etc* […] *he is a professor in psychiatry and he is very interested in the research on …erm… you know, I think he is especially interested on researches on medication, how they are published how journals report results…you know like they will say …* [unclear/inaudible*] score and this and that* […] *like sometimes they will report an improvement of 10 points but in real life it makes no difference* […] *he's got some other friends who also do a lot of research, so any article that comes though he will email it and we might have an email discussion.* […] *he will only circulate stuff that the thinks it's worth circulating."* [mid-career consultant]

> *"it's a regular occurrence, we have journal clubs every Monday; so some journal club will come up, somebody will talk about drugs, very useful* […] *you are not just relying on, say, one journal or…something like that you have the opinion of peers and then this is very evidence based. Plus you have your own journal, psychiatric journals , you have BMJ, you have lots of sources of information. Then you can collect that up and keep an eye. I think you can see which drug will help your patients."* [mid-career consultant]

> *"The other option I think about in her case is a drug called* [generic drug name (typical)]. *It's also again an older drug, it was produced first in the early 70s, erm.. it's a drug that some of the staff figure is too gentle, as it were, that they are not absolutely convinced that it works* […] *they are not actually sure it's that effective."* [senior consultant]

> *"No good reason to go for one over the other, but I'm aware from the Maudsley guidelines…that is what I would do if I was pushed*" [nurse prescriber]

As a serendipitous finding, one consultant mentions that staff are inclined to measure drug efficacy by its resultant side-effects.

> *"*[generic drug name (typical)] *– is an old drug that was produced in the late 60s. it's a European antipsychotic, not available in the US, but it's one of the drugs that I would use the most.* […] *they* [other staff] *like to have the reassurance that the drug is*

> *working that seems to me at times that they like to see it causing side-effects. So there is a little bit of bias about a drug like* [generic drug name (typical)] *with a number of people figuring that …well they're not actually sure it's that effective because it doesn't cause too many in the line of side-effects."* [senior consultant]

It is an intriguing possibility that, given the caution developed over side-effects, clinicians find inconceivable that efficacy can be obtained without the patient suffering some adverse effect.

Sub-theme: where research evidence is an important contributor to clinical expertise, clinicians tend to prescribe to patient's presentation and circumstances.

Most clinicians who mention research evidence will then make the prescribing decision based on what they want to achieve, given the patient's presentation; their perspective on evidence can be divergent, but these participant recognise the importance of keeping-up-to-date:

> *"I think erm, you'd have to be confident in looking at the research evidence"* […] *"if I was prescribing a drug like that I would be very wary of side-effects… there is a possibility for a female if you prescribe* [generic drug name (atypical)] *or* [generic drug name (atypical)] it can raise the prolactin levels so that would be something to be careful [nurse prescriber]

> *"The clinical trial evidence about what they do and don't do is close to worthless"* […] *"I'd be very concerned about a girl like this because, … we need to get the treatment right early on, we don't; want her to escalate, we don't want her to be on anything longer than she has to be on, and the goal would be trying to get her back to her course in Cardiff"* [senior consultant]

> *"When I chose an antipsychotic I go quite strictly with the available evidence"* […] *"I am also aware that we do have situations where an individual might respond to a specific antipsychotic even though its overall efficacy isn't very good* […] *I would be looking at* [generic drug name (atypical)] *or* [generic drug name (atypical)] *as agents of first choice because they are most efficacious and they happen to be quite different in their receptor profile. I would have to find out whether she is particularly paranoid because in my experience if paranoia is an issue.. out of* [generic drug name (atypical)] *and* [generic drug name (atypical)] *I would choose* [generic drug name (atypical)] *as the dopaminergic agent. If I have a potential weight problem, then I would choose* [generic drug name (atypical)]. *If I wanted to get some possible weight gain and if I needed sedation, I would certainly go for* [generic drug name (atypical)] *as the first choice.*" [senior consultant]

> *"I know it's a word, psychosis, but the psychosis and the effect on the person is different, and the choice of antipsychotics is based on presentation: Does he need sedation? Does he need immediate action? Is the risk contained? What type of route of*

> *antipsychotic would you follow? Will he take, will he accept it? Is he able understand your perspective?"* [early-career consultant]

By contrast, clinicians who do not mention that research hand guideline are of particular significance to their practice have displayed a prescribing 'routine' as if preference for a drug is so engrained in their clinical experience that a reductionist view is applied to patient presentation almost akin to fitting a patient into a template of presentations.

> *"ok, what I tend to say is like this is the medication we have to help you and we've used it on different people and they responded and this works with psychosis"* [foundation year doctor]

> *"so yes what experience you have with an antipsychotic is … is bound to choose them more* […] *that experience gets reinforced"* [early career consultant]

> *"The first step is probably looking into what the literature is telling me that works better, the second step* […] *is a bit of a mixture between what I want to achieve, what the patient wants to achieve,* […] *and we just tailor the choice really, if the medication is necessary."* [mid-career consultant]

This sub-theme is important as it demonstrates that research evidence forms an evaluation spiral which allows to build experience based constant assessment of dynamic patient presentation and adjust treatment based on addressing emergent symptoms.

<u>Theme 4: Trade-off between efficacy and side-effects determines the choice of treatment</u>

This theme revolves around clinician's beliefs on the balance and compromise required between achieving clinical efficacy and safeguarding against the impact of side-effects. There is a trend that highlights that beliefs about efficacy and risk are informed by own clinical experience, and to a lesser extent by research evidence. Clinicians who are less risk averse and who take the responsibility for prescribing without necessarily relying on a collaborative approach, and who refer to either their own clinical experience or research evidence indicate that efficacy is the most desirable outcome:

> *"Don't do a trade-off between side effects and efficacy. What I say is that erm ... most ... most patients are willing to put up with significant side effects if the efficacy is good. And they're not willing to put up with side effects if there is no efficacy"* [mid-career consultant]

> "[…] *because patients seem to want efficacy, I look at efficacy data for antipsychotics primarily, and not just from my own study, but from a lot of very good recent meta-analyses"* [senior consultant]

> "*I would go for clinical efficacy* […] *it's likely and hopeful that the patient may be taken off the drug erm, at a future stage, ... when they appear to be making more progress.* […] *there may be short term weight gain and sedation, but the research says that patients who put on weight actually are more likely to respond to medication"* [...] *I think that is something that you have to accept really if somebody is severely unwell"* [mid-career consultant]

> *"although I look into evidence and I always take into account that I don't want to give medication that is very little efficacious."* (sic!) [senior consultant]

> *"So basically ... I would be looking at* [proprietary drug name (atypical)] *and* [proprietary drug name (atypical)] *as agents of first choice because they are the most efficacious, and they happen to be quite different in their receptor profile. So it's quite good to have one very dopaminergic drug and one multi receptor drug, and to use those as the two first choices. So in this patient I would probably go for* [proprietary drug name (atypical)] *as the first choice err, because it sounds more like a general psychosis and not necessarily like a particularly paranoid picture."* [senior consultant]

For clinicians who rely more on others in the decision -making, and who perceive risk as a major factor, the patient management revolves around ensuring that side-effects are contained.

> *"I really have problems with* [proprietary drug name] *and* [proprietary drug name] *because of the horrific weight gain and the metabolic syndrome, err, and that's a very important factor for me* […] *the idea of making people fat with the drugs that we use* […] *is a very depressing thought for me, and I'm not even the one that has to take it."*[foundation year doctor]

> *"...but if I was prescribing a drug like that I'd be very wary of side-effects, monitoring side-effects, you know, erm.. akathisia, dystonia..* […] *I think it would need a multidisciplinary approach really to deciding..."* [nurse prescriber]

> *"she's a woman so I wouldn't particularly want her to go into anything that caused a huge amount of weight gain"* [senior consultant]

> *"depending on what ward she's in, they like to have the re-assurance that the drug is not causing side-effects"* [senior consultant]

> *"definitely not consider erm..a typical antipsychotic, because I believe there is more side-effects in relation to that"* […] *bearing in mind I wouldn't go down the route of just immediately prescribing, there is side-effect of something, I'll measure it by the side-effects, age* […]*, things like weight gain, it's the all important things that are self-esteem related,* […] *you don't want to give a client who already has a psychotic illness further problems physically.""* [other nurse prescriber]

> *"looking at the metabolic profile, she should be able to tolerate [proprietary drug name] more than anything else, the reason being because of metabolic side-effects than anything else* […] *amongst atypicals also there are some drugs which are more harmful, and actually they will* [unclear] *metabolic syndrome, so I make them well but I kill them by giving them heart failure, heart problems. That's the problem. So they die under twenty years of age; they've been well but they die younger, twenty years of age because of err, psychotic ... bad physical health problems and antipsychotics."* [early career consultant]

> *"I have a very low threshold: if a patient develops side-effects, young patient, I will instantly take them off the medication."* [mid-career consultant]

> *"*[…] *which one caused* […] *much side effects imminently ... so I know like [proprietary drug name] causes weight gain and diabetes, but we'd think* […] *... these are a bit more safer."* (sic!) [mid-career consultant]

> *"Erm ... the efficacy is ... broadly speaking about the same for most of them, I think where they differ is in terms of their side effect profile, and in terms of what may or may not be an acceptable side effect profile."* [senior consultant]

It is interesting to note that when discussing risk factors associated to side-effect, most participants mention metabolic side-effects; moreover, the discussion seems to be very polarised: therapeutic solutions seem to focus either on efficacy or on mitigating for side-effects, with very few views on the balance to be achieved.

Sub-theme: Attitudes and beliefs regarding side-effects stem from emotive views on iatrogenic harm

The data above also point to the fact that there is an emotive link between the way side-effects are perceived and iatrogenic harm: participants indicate that they feel a personal responsibly to not cause further problems for the patient, indicating that symptom reduction is viewed as short-term which will be outweighed by the long-term impact of either extrapyramidal or metabolic and/or cardio-vascular side-effects:

> "C*olleagues might say, put them on* [generic drug name (typical)] *and* [generic drug name (typical)] *they have patients who are stiff and rigid and, shuffling. […] I say, you may be better symptomatically but you have other problems.* [senior consultant]

> *"According to me diabetes is the worst thing; cardiovascular problems are the worst thing* […] *big studies like CATIE* […] *things coming out and saying, hold on, not a lot of evidence,* […] *more of side effects with the atypicals, you think that they are very cleaner drugs; no they're not."* [early career consultant]

One participant identified clearly that efficacy needs to be meaningful and worthwhile for the patient to warrant the risk:

> *"these things have awful problems linked to them for the most part. So really you have to feel a benefit, to make it worthwhile to take the risks that we're going to take."* [senior consultant]

Participants' own interpretation of research evidence is named as 'the reason' to ponder the implications of side-effects over considerations of efficacy:

> "*there's a bunch of these drugs, thirty-odd drugs* […], *the clinical trial evidence about what they do and don't do is close to worthless"* [senior consultant]

> "*you're left making your decisions largely on the basis of what's acceptable to patients*, *as opposed to having something that you can say necessarily works an awful lot better."* [mid-career consultant]

Theme 5: Person Centred Care is genuine but "patient involvement" can be tokenistic

This theme explores the cues that prompted engagement with the patient and what is the nature of information sought from the patient, and whether this contributes to a significant extent to decision-making. Unanimously all participants named patient-specific factors, such as clinical presentation and patient circumstances in their assessment, but the weight attributed to these factors is variable. All participants rely on the patient and/or family/carer to obtain more information around the presentation and circumstance, but only some participants actively involve the patient into the decision-making. This seems to correlate with individual attitudes and belief and to some extent with the clinician's experience:

> *"*[…] *get to know her a bit more, and maybe get to chat to the… rest of the family, or perhaps.. let us know what she's normally like* […] *you'd also want to have input from the rest of his family or friends, or whatever, on issues like this, like should he be* […] *staying at work, or in the job he's in."* [senior consultant]

> *"Because if the patient has developed side effects with 300 of* [generic drug name (atypical)] [8] *that means there is a long-term complication of tardive dyskinesia, you know, all kind of neurological complications which we don't want. And his job involved standing for long hours silently and still, so how can he have akathisia and ... do the job?"* [foundation year doctor].

> *"you'd want it care co-ordinated, you'd want people doing psycho-education work with him, you'd want people ... to perhaps ... looking at his social and occupational needs."* [early career consultant]

Empathy and therapeutic alliance is a determinant factor in collaboration, for participants for whom side-effects play a major role in the therapeutic decision:

> *"*[…] *structure and a routine, that's she's getting reasonable food…, and its warm. And who knows what she's been through; we don't quite know what she's been through to lead her to ... be here, but we can certainly try and make sure that she's looked after here.* […] *simply telling his story may make a big difference to him. Seeing it written down by me, seeing what a third party hears when they hear the story err, can make a big difference to him."* [senior consultant].

> *"I see it as my ... as a personal strength that in that situation* […] *because of the respectful way that I deal with patients, I'd be able to talk to them, go through my reasoning* […] *in as much as it is,* […] *when you're prescribing a drug to a patient you've got to discuss it with them, you've got to ... talk about their hopes, their fears, their expectations, and especially with major drugs like antipsychotics."*[…] *"so really the important thing is an engagement. I think if you get a relationship right with the patient ... especially in such a scenario, then you are like, you know, your likelihood of success is better in the sense that, you know, you want the patient on your side."* [foundation year doctor]

> "*sometimes, you know, erm ... I believe if ... if they* [the patient] *feel that something's going to help as well its half the battle* […] *my view on prescribing is that they will always have, erm… options, okay? And I will present them with err, leaflets on each drug, go through the side effects; I believe that ... that's important, when to take it, how to take it, so I never prescribe without patient information leaflets being available."* [nurse prescriber].

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[8] This was a surprising statement as published literature shows that at low dosage (< or =300 mg/day) [proprietary drug name(atpical)] the incidence of extrapyramidal symptoms was comparable to placebo (Curran & Perry, 2001). Neuroleptic malignant syndrome is mentioned more often as a risk (Musshoff, Doberentz, & Madea, 2013), therefore muscular rigidity and autonomic dysfunction may indeed have been a consideration.

> *"And, again, you know, usually we say, you know, you offer either oral ...a tablet or an injection, depending on what the patient would prefer"* [mid-career consultant].

There is however a limiting factor: participants who mentioned that efficacy is more important than side-effects tend to limit the scope of patient's involvement:

> *"Erm, if there were issues around compliance, or they expressed a preference, and I probably would mention these quite early in terms of treatment erm, and offer them a long acting injection."* [senior consultant].

> *"But normally what we say, like sometimes they don't take the medication and ... because they are ill, so … then it would ... if she's* [unclear] *like we could go for IM injections and all that, like in* [proprietary drug name (typical)]*", that is one we use, or* [proprietary drug name (atypical)]" […] "*And some people don't want to take it, and they might say like they are taking it, and if they ... if you don't know of course we can change it to depot and ..."* […] "So *we would do the drugs screen and all that, check it out, if he's taking it but he's not responding. And, again, patient compliance, if he's not going to take oral we go for depot quite a lot."* [foundation year doctor].

> *"sometimes, when they are too ill, they don't communicate much, so like, so they don't know… they are not able to make decisions"* [foundation year doctor].

> *"that has been repeated in a number of studies, … in stark contrast with clinicians who seem to put side-effects as their main priority and efficacy much lower down the list, we have an immediate discrepancy here between what most patients want as their top priority and what clinicians think their top priority is"* [senior consultant]

Strong views and beliefs feature prominent in this discourse, particularly when it's felt that allowing too much patient choice will undermine professional authority or the patient's perception of clinician's expertise:

> *"My personal view would be erm, the consultant should erm ... have the major say because it's based on years of experience in treating psychotic behaviour with medical expertise* […] *I think if we start giving patients choices of tablets they should take its ... you may give the impression that erm ... we're not exactly sure which is the best drug and erm ... and the patient may be left with the idea that erm, we're not one hundred percent certain, you know, which will be effective and which won't be really"* [nurse prescriber].

> *"*[…] *but I think if it came down to myself, I would be happy for my doctor or prescriber to tell me what he thought was the best drug and I would ... I would go with his advice really."* [foundation year doctor].

> *"I would sort of be quite clear to the patient, if you start listing drugs one by one and looking at the pros and cons of each one, again, patients may think that erm, it's almost a lottery erm, which drugs are effective and which ones aren't as good."* [mid-career consultant].

> *"So I was always say to patients that erm, when we discuss the choice of drug, that I would like to give them one of the two that I consider to be the most likely to help them. And so those two that are likely to have the highest efficacy. And then I discuss the quite different side effect profiles with them and see whether they have a choice, or a preference, and if they haven't I would make that choice on the err, on the individual situation, based on the individual situation of that patient."* [senior consultant].

> *"I've got more psychiatric experience than the patient has…what I would do here, I would first* try [generic drug name (atypical)]*"* [mid-career consultant].

Sub-theme: involving the patient in the prescribing decision is a way to mitigate risk

The degree to which the patient is involved in the decision-making process can vary; factors that seem to influence the level at which patient involvement is sought.

The risk of iatrogenic harm (i.e. from side-effects of the drug) is mitigated by discussing this with the patient and achieving a consensus treatment plan.

> *"I would try to …erm, the broad message would be something on the lines of look, erm..* […] *these things have awful problems linked to them for the most part. So you really have to feel a benefit you have to be able to pick out something useful this thing is doing for you to make it worthwhile to take the risks that we're going to take* […] *it's more of a case of trying at the start, not so much as listing all the awful things that can happen, but just sayig , look, you know, there is a big ling list of awful things that could happen, and you may get even ones that aren't on this list. It's only wohrtwhile doing it if you can pick out a benefit. At the end of the day you need to be the one who's making the call that you're getting a benefit, and the benefit is worth the problems that you may also be having"* [senior consultant]

> *"then I asked him: do you want to choose? But I resist the urge to make a decision, unless the patient can't make a decision.* […] *I will first offer the patient the options. You need to have a good relationship … If you have a good relationship then your treatment will sort itself out, and you are keeping the patient safe. So what I normally do I tell the patient that, you know, there are medications, and there is no right or wrong medication, usually you do your research, you decide, you look at the ide-effects, you look at the complications, common side-effects, rare side-effects and then you decide which drug would you be willing to put up with* [mid-career consultant]

> *"If you are looking at long-term treatment it is always good to make a decision with the patient* […] *what is the point of you having the information, you have to be able to offer it to your patient and they can make a decision"* [mid-career consultant]

This sub-theme shows that clinical experience with the condition is used in conjunction with the patient's choice or informed by the patient's perception of efficacy and trade-off with

side-effects; this can be interpreted as either a deliberate attempt to develop a treatment plan in partnership with the patient, or to give patients as much information to support them to make an informed decision; in this case the onus is put on the patient to make that choice and take the risk that is acceptable to them.

Theme 6: Perception of risk acts as good indicator on the bounds of patient management

The theme explored the different natures of risk, the cues that prompted participants to evaluate risk, the way in which risk is manifested in decision-making, what are people focusing risk on. There is variation in importance attached to risk, in the attitude to risk, and this is carried thought in the way in which patient management is later formulated.

Risk relating to presentation revolves around understanding whether this is immediate and therefore there is an urgency to act, or there are concerns around the presentation that warrant a risk assessment.

This this consistent between participants, but people are doing it in a variety of ways, there is a variation on how risk is evaluated: for some it is more important, and those participants have focused predominantly on risk, whilst others are more attuned to risk, which means that 'risk' and how its's managed will be different between participants.

Sub-theme 1: Mitigating risk by seeking additional information

For participants for whom risk is a major consideration, the key part of work in decision-making revolves around presentation and information seeking; there is a link between attitude to risk and the context in which risk is managed: the risk participants talk about in the presentation reflects in the way in which they think about managing the patients which is all about containing this risk. Information seeking is a key defining feature: in the think-aloud

exercise these participants talk at large about seeking information from the family, from the GP, seeking monitoring from the rest of the clinical team.

> *"It all depends on the risk… how much are the risks… and how you feel and how is the behaviour of that person that drives a lot of prescribing"* [early-career consultant]

> *"if the risks are contained, if the behaviour is known … because it's … do you actually immediately need to treat or do you need to have a psychological input… the you would go the other route…[…] I would like a proper demographic… thingy… on my patients before prescribing, looking at the family histories and things. And looking into any predisposing factors which are going to make things more worse* [early-career consultant]

> *"but here the risks are quite high, it's quite clear* […] *presentation… this gives me a bit but it does not give me a lot, I would like a lot more information, has she tried anything in the past, is she known to the GP, I would like to know before deciding* [mid-career consultant]

> *"Erm.., and obviously, you know, in terms of suicide, I would have to make sure that she's safe, and maybe has had a one-to-one* […] *I am not sure that I would go in immediately* […] *I'd want here to be monitored, check her sleep patterns, how distressed she would be on the ward* […] *I'll be wanting to gather more information*" [nurse prescriber]

> *"but we also have to make a safe choice* […] *in these circumstances it's all about immediate reduction of risk, of symptoms* […] *I need more history to know what is the diagnosis, I'd need to check whether she's been tried on something … has responded to something*" [foundation year doctor]

Sub-theme 2: Attitude towards risk informs decision-making

The more risk averse the clinician the more caution transpires in decision-making; the way they mitigate risk is by seeking a lot of information in what appears to be a way to manage the risk. None of the information will however, ultimately play a definitive role in the decision-making, which is either relied upon then on multidisciplinary team, on peer-support, or is planned exclusively around containing risk rather than clinical efficacy.

> *"I'd want to be very, very careful* […] *putting her* […] *on any pills at all.* […] *I think it would be good to ... get her seen on the ward for a period of time, for a few days at least, without her actually being put on anything at all. For us to get a feel for just what's actually going on and what she looks like without treatment."* [senior consultant]

> *"If you want to know how I personally assess people* […] *I am very pedantic in following the college format in history taking, so I do all the headings, even nowadays. I have a sort of mental map that I follow, and I class the symptomatology into mood,* […] *psychosis, anxiety, and obsessive compulsive. And I always ask about risk."* [other senior consultant]

> *"in letting the person go and to be reviewed a week later I'd need to be clear from a risk-assessment point of view that there isn't any potential, really, that he may cause harm to the girl or even himself."* [nurse prescriber]

> *"this is a valid case for doing nothing in terms or… or just monitoring. So it would depend on what the risks were and what the distress was."* [senior consultant]

The assumption above that the assessment of risk caries through to the way in which the patient is managed holds true for participants who did not deem the patient to be at risk; participants who decided they can manage the risk required less additional information and made a swift treatment decision.

> *"I'd probably use one of the better tabs,* [proprietary brand name], *quick hit things, to know the risk is contained* […] *you'd want to know that someone is responding to treatment and oral medication's much quicker."* [other senior consultant]

> *"So, that's a different kind of … suicide risk. So I think we need to understand* […] *why the suicide risk thing came into the picture.* [mid-career consultant]

> *"it depends on the risks, obviously consider against the Mental Health Act in relation to the risks and you know, whether we can manage this in the community"* [nurse prescriber]

> "[…] *in these kinds of circumstances err, it's about… immediate reduction of risk, symptoms,* […] *we are looking at containing the situation"* [senior consultant]

This means that there is a theoretical link between categories: risk aversion leads to caution in decision making and reliance on others. The treatment plan revolves around containing risk and not necessarily around clinical outcomes.

Discussion

"The decision remains essentially based on the clinician's skill to elicit from the patient a veritable account of their subjective experience and, in the ideal case, to apply a kind of Bayesian prior probability–posterior probability reasoning, supported by learned and stored information, in order to arrive at a […] choice of treatment" (Jablensky, 2013)

The results highlight important aspects of the clinical decision-making process. All the themes identified in this study map onto factors of the EBM model developed by Haynes et al. (2002), providing validation of these factors, but added to literature by exploring how weight is attributed to various factors, how do they interact and what generates influencers. The study started from the assumption that some factors other than guidelines influence prescribing behaviour, or some of these factors influence how guidelines and research evidence are adopted - as empirical evidence highlighted that prescribing trends do not follow research evidence and clinical guidelines.

Six salient themes emerged from the data analysis:

- The extent to which the ownership of decision-making rests with the clinician, or on a collaboration with colleagues – with different levels of responsibility accepted for different stages of the process, and opinion leaders are relied upon to process and interpret research evidence;
- The scope and value attributed to information depends on its source; normative values and beliefs determine the action taken;
- Confidence /reliance on research findings and guidelines is based on anecdotal validation rather than individual critical appraisal

- The choice of treatment is informed by clinician's beliefs on the compromise required between achieving clinical efficacy and safeguarding against the impact of side-effects.
- Whilst the adoption of a Person Centred Care model is genuine, 'patient involvement' is limited to generating therapeutic alliance.
- Perception of risk is good indicator of treatment choice and containing risk is a priority over clinical outcomes.

The results are comparable to earlier findings by Baiardini et al., (2009) that knowledge transfer depends on clinicians characteristics, not only on guidelines themselves, nor solely on the social and cultural context or the implementation framework/strategy used to disseminate the information. Clinicians' knowledge (research evidence and clinical guidance), behaviour (treatment routines and patient management) and attitudes (such as modelling on influencer peers, the views and feelings on the trade-off between side-effects and efficacy, or patient involvement) influence clinical decision-making.

In addition, this study highlighted as a unique contribution, that different participants place different weighting on each aspect and factors are not clear-cut and distinct from one-another, but they merge and intertwine: clinical experience is shaped by values and beliefs and informed by patient factors and by research evidence, either directly or indirectly thought collaboration with others. The interpretation given to patient factors (clinical presentation and circumstance and patient preferences and actions – as defined by the EBM model) is subjective and informed by clinical experience. The value assigned to each factor depends on its provenance, and research evidence is trusted less than opinions of senior colleagues.

The first theme highlighted that taking ownership of the process does not depend on clinical experience but on normative values and beliefs; collaboration with peers is relied upon for

different parts of the process, not necessarily for the whole treatment plan; clinical experience resultant from previous patients dictates treatment pathway but the onus of deriving research evidence is placed on others. Senior clinicians with confidence in their clinical experience refer may collaborate with colleagues to gather further information about the patient or to monitor the patient. Clinicians with less confidence in their clinical experience, irrespective of the level of seniority, will put the onus on others to make decisions, and will look at collaborators as a useful resource on research evidence and information dissemination.

The reliance on colleagues detracts from the focus on evidence appraisal and integration, as practicing Evidence-based medicine is assumed to reduce tacit reliance on the knowledge of eminent peers (Djulbegovic & Guyatt, 2017); this reliance is also apparently true for non-medical prescribers, as illustrated by the themes above, and this is supported by a study by McIntosh, Stewart, Forbes-McKay, McCaig, & Cunningham (2016) which highlights that among nurse-prescribers, peer-support was relied upon in decision-making, but prioritization of experience and peer conflict were negative influencers to taking ownership over decision-making.

The gathering of clinical information is another factor discussed by Haynes et al. (2002) and this is assessed in the themes. Many participants were happy to take ownership of the information gathering process and/or recognised its importance in collaborating with other professionals in creating a comprehensive assessment of the clinical picture or a treatment plan. Bradley (1991) suggested that prescribers seek additional information for high-risk clinical scenarios or high-risk treatments; participants who identified more risk with a clinical scenario and the valued primarily the wellbeing of the patient wanted more information and discussed diagnosis in further detail. Haynes, Devereaux and Guyatt (2002) stated that clinical expertise will ultimately be the deciding factor in integrating all the information to come up with a treatment plan - and this was upheld by the themes that

emerged in the current study: many participants relied on their clinical experience, but the main finding here was that professionals place great importance on what has worked for their previous patients. This is a worrying trend as it limits clinical experience to a retrospective analysis of what has worked with previous patients, thus making it hard to integrate new information from research, and is supported by Banning (2007) which shows that with experience, decision making becomes instinctive and professionals will rely less on guidelines.

The themes supported the evidence for both the intuitive-humanist decision-making model and information-processing model: the second theme that emerged related to information seeking and processing and it links closely to the theme on risk analysis. The study showed this to be a linear process: whilst participants rely on others to generate the information they require to be able to make a decision, the source of the information plays a major role in establishing its validity and its value.

The first suggestion that clinician-generated information is attributed more weight appeared in relation to information sought for diagnostic purposes; a lot of supplementary information was required to reach a diagnostic decision and rule out a differential diagnostic - and understandably at this stage the information elicited from the patient directly could be of limited value. This theme however, also illustrates the belief that the patient's perspective is more fallible than clinician's expertise. The first example to support this relates to a very polarised view in relation to efficacy and side-effects: clinicians seem to hold the view that patients can either achieve efficacy and tolerate side-effects, or the treatment should be devised to prevent side-effects from happening, even if this is at the expense of efficacy. This view is then presented to the patient as the framework in which the choice has to be made, and the whole discussion with the patient in the context of shared decision making is centred

either around efficacy or around side-effects. The second example comes from a self-assurance displayed by some clinicians that either they have more expertise in psychiatry than the patient or that their place is not necessarily to submit to patient's wishes. This is discussed more widely under the theme relating to shared decision making.

The perception of risk seems to dictate how much information participant want before they are able to make a decision and also is a good indicator that risk-averse people will seek a lot more information to mitigate this risk and will rely on peer-support for the decision-making process. The therapeutic decision also revolves around mitigating risk rather than on efficacy of treatment.

Risk relates closely to the volume of information sought and to the nature of the source of information. This corroborates the results of a study by Jones, Greenfield & Bradley (2001) who discovered that the degree of perceived risk will influence the clinician's decision and once a higher risk is assumed, the sources of information tend to go up in both number and hierarchy. For low and medium risk situations the GP was relied upon as source of information, whilst for high risk situations the reliance was on senior consultant colleagues.

The role of research is again highlighted in the theme discussion the compromise between side effects and efficacy of antipsychotics. This issue has been discussed in multiple reviews including the CATIE (Lieberman et al., 2005) and CUtLass (Jones et al., 2006) and whilst there is still much debate regarding the comparative efficacy of different antipsychotics, there is a definitive consensus on side effects associated with particular antipsychotics. Participants for whom adverse reactions are a major factor appear to more risk averse. Some earlier research evidence - to which the present study can relate by extrapolation - discussed the relationship between prescriber's perception of risk in relation to willingness to prescribe new drugs /adoption of new drugs (Coleman, 1967; Bradley, 19991) but there is a novel element in this theme that relates clinicians' interpretation of risk

to the choice of medication and how this choice focuses on efficacy of the drugs or on their risks.

The results of the present study are also in accordance to earlier findings that shared decision-making is influenced by both clinician and patient factors and it is not always an appropriate model of care in psychiatry. Shepherd, Shorthouse, & Gask (2014) highlighted the need for psychiatrists to recognise how and when the patient should be involved, based on the patient' expressed wishes on whether they want to assume responsibility for their care, or on their perceived level of capacity/competence. The authors also note the need to recognise that the binary model of patient either having or lacking insight into their condition is not appropriate and a dynamic model should be considered, as capacity fluctuates. The theme discussion patient participation in decision-making explored the models of involvement and highlighted that the paternalistic model, by which the clinician takes responsibility and the 'expert patient' model co-exist in clinical practice, as previously proposed by Charles, Gafni, & Whelan (1997). This theme's novel contribution consists in demonstrating that the major contributing factor to an informed decision model is clinicians' perception of risk relating to side-effects and the use of collaboration with the patient as means to achieve efficacy by ensuring treatment compliance. The theme also brings a different perspective to Seale, Chaplin, Lelliott, & Quirk (2006) who perceive discussion about side-effects as a concern - as it conflicted with the clinician's desire to promote antipsychotic medication as the "mainstay" of treatment in schizophrenia: clinicians in this study saw discussing side-effects in detail and at length as an empowering action. Similarly, the same study found that clinicians are apprehensive that negative information about side-effects will affect patient's motivation to take the medication – whilst this theme shows that clinicians see this openness about side-effects as means to secure therapeutic alliance and therefore adherence to

treatment, and is supported by the argument made by (Hamann et al., 2008) that patients who felt they were not involved in the decision-making process tended to be more non-compliant. In the least, this theme makes the case for patient-centred care and shared-decision making, and opens a few avenues to explore in this context. One of potentially interesting area would be to explore how patients' 'insight' into their condition can be assessed more accurately that by the simple four step test for capacity mandated by the Mental Capacity Act, and how can it be enhanced to enable a fuller participation into the decision-making. Another interesting topic would be to examine whether there are differences between the stated intentions to involve the patient and the practicalities of everyday clinical care; this is particularly interesting as the theme in this study showed that the main path towards patient involvement is to discuss treatment options and side-effects of medication, but a previous study showed that doctors find difficult to provide accurate/detailed information about side-effects, either because they do not have sufficient knowledge or because in the realities of clinical situations it was impossible to find the time to discuss them at length (Seale et al., 2006) and practical methods for building therapeutic alliance are in fact rare (Awad, 2000; Cruz & Pincus, 2002)

The fifth theme that emerged related to how research evidence is acquired and used. Most participants mentioned that their practice is informed by research evidence but only some were able to substantiate that with robust critical appraisal informed views and relied on knowledge disseminated by colleagues to build research evidence into their clinical experience. Although evidence was supposed to play a central role in practicing Evidence Based Medicine, only a few participants in this study indicated how they would embed evidence in their practice. Some made reference to information acquired from research evidence but struggled to make unequivocal statements to indicate the exact source of evidence, or critically examine the validity and flaws of the evidence (apart from references

to common knowledge that evidence relating safety and efficacy of antipsychotics was flawed or not always reliable.)

A sub-theme identified that clinicians who mention research evidence as an important contributor to their clinical expertise tended to prescribe as to achieve a particular therapeutic goal, based on patient's presentation and circumstances. Most clinicians mention research evidence in the context of clinical trials. Only one participant mentioned research evidence in relation to patient preferences, and no qualitative research was mentioned in relation to 'evidence'.

This theme was important as shows that research evidence is actively used to build clinical experience - irrespective of whether this was acquired first-hand or by proxy dissemination via colleagues and journal clubs. By contrast, clinicians for whom evidence is not an essential factor tend to form a 'routine' prescribing of a 'favourite' drug, for all the patients who fit into a 'template' of symptomatology. Given the categorical model of diagnosis in DSM-IV that most clinicians (who have been interviewed) have been trained to work to, this is not a surprising finding. From the former category, clinicians whose priority lay around efficacy rationalised their prescribing choice to the patient's presenting pathology and linking the drug of their choice to potential benefits that could be achieved by this drug. Conversely, clinicians who focused on preventing side-effects, linked research evidence to justifying how the use of a drug would prevent an undesirable incidental outcome. The wider implications of this theme are that prescribing is based more in clinical experience and trial/error methods than on evidence, but clinicians do not want to be seen to support non-evidence based prescribing. Connolly & Taylor (2014) stated that clinicians are reluctant to prescribe in a non-evidence based way, as their prescribing is audited and they are subject to peer-pressure, but this practise may stem from poor response rates and generally the limited choice of efficacious antipsychotics, which is also highlighted in Lally & MacCabe (2015).

Additionally, whilst several participants use research to guide their practice, only three participants said they would actively refer to the guidelines when prescribing – and this lack of implementation highlights the importance of this study's research question. The findings of this theme connect to Rowlands' (2004) findings that a that a strong clinical lead is needed to disseminate evidence and encourage its use, and to McGettigan et al.'s (2001) study who identified social interaction as the preferred method of transferring information. As previously discussed, McGettigan found that senior colleagues were the prominent source of information in relation to a drug, followed by hospital meetings and journal articles. In correlation to these two studies, the theme suggests that there may be more to be explored in relation to how knowledge diffusion works in practice. It is interesting to note that Jones et al. (2001) propose that attitudes and beliefs are shaped by social networks and will be a crucial determinant of knowledge adoption, in a process reminiscent of the "accelerated contagion" coined by Coleman in 1967. As Coleman demonstrated that influencers were early adopters of new knowledge, this theme brings evidence on the potential impact of seeking influential peers to facilitate building clinical expertise.

In the classical model of diffusion of innovation, Rogers (2003) established that a successful knowledge translation will take into account the individual local scenario. As Guidelines are released nationwide and each NHS Trust will establish its own implementation strategy, the findings of this study allow the hypothesis of a potential new model of knowledge translation, by using early adopters as influential peers.

The participants in this study did not mention organisational issues or cost effectiveness, which have been identified by Forsner et al. (2010) as barriers to guideline implementation, and this may suggest that while these barriers are important at organisational level, they may have little impact on daily prescribing.

Limitations

A number of limitations that might affect the impact of this study's results are related to the methodological approach and are inherent to qualitative research in general and to thematic analysis in particular. Other limitations stem from my own ontological position.

Morrow and Smith (2000) identify that qualitative enquiry is underpinned by the paradigm to which the enquirer subscribes and the standards of 'goodness' or quality and 'trustworthiness of a study are paradigm specific (Lincoln & Guba, 1986).

My own perspective and ontological 'affiliation' is firmly anchored in positivism – therefore the way in which the study was designed and set-up sought to enable outcomes to be scientifically verified or capable to withstand logical or mathematical proof. Thematic analysis as a qualitative methodology is also rooted in positivism and therefore the 'trustworthiness' criteria should not have been on conflicting positions with my own views but two issues arise from this perspective:

The first is that by following this parading some of the quality criteria that are specific to say constructivism (such as fairness, ontological authenticity and meaning) cannot be applied to 'measure' the 'goodness' of this study.

The second issue is that learning and conducting a qualitative enquiry when one's own mindset inherently chases quality criteria specific to quantitative methodologies is bound to stray from the 'purist' qualitative view.

This chapter aims to describe how these were recognized and the degree to which they could be addressed.

Morrow (2005) describes that trustworthiness of a qualitative study is assessed by considering the social validity, subjectivity and reflectivity, adequacy of data and adequacy of interpretation as transcendent criteria and credibility, transferability, dependability and confirmability as positivist paradigm-specific quality criteria.

The social validity is an issue of subjectivity and for this study it starts with the research hypothesis: the issue that clinical practice does not reflect the NICE guidance was based on anecdotal evidence at the start of the study and a precursory chapter was required to ascertain whether this is indeed the case. However, the social validity reason as non-adhere to guidance has not been explicitly communicated to interviewees as to minimise 'desirable answers' - but this in turn may have had the unintended consequence that respondents might not have seen the real social and scientific value of the study and might not have approached the interview wholeheartedly.

Subjectivity is in the very nature of the data collected and the analytic process , and Morrow (2005) suggests that this might be limited or embraced, depending on the paradigm to which the researcher subscribes: in this case, as a positivist qualitative researcher I have used strategies that are familiar to quantitative methods (such as independent auditor and frequency tallies) to minimise bias. One such strategy also involved making ones' own assumptions and biases clear to others – and this worked well in the development of this study: as a novice to qualitative enquiry I was unable to use reflexivity models rigidly by keeping a self-reflective journal or an ongoing record of my experiences as this felt awkward unnatural and synthetic; instead, I used a 'community of practice' (Rossman & Rallis, 2003) in my thesis supervisors and my peers to engage in critical discussions of the interview material which helped reduce to some extent the tendency to add my own interpretation to themes. It is of course impossible to be completely impartial when analysis data and it must be said that the conclusions presented in this study are reflecting my own positivist position. Similarly, methodologically the positivist view led to a need to look at the themes derived and want to 'test' these as a hypothesis to establish whether there might be a degree of generalisability that could be worked on.

However, being a novice to the method has its advantages: as a newcomer I looked to the 'instruction manual' for every step of the way – and the quality prerequisites were buit-in. In the first instance, the flexibility of iterative thematic analysis as a method makes it difficult to decide which aspects of the data to focus on. With an abundance of categories of codes, it can be a dauting process to select those that present sufficient characteristics to constitute a theme and then reduce broad sweeping constructs to a focused narrative. Although thematic analysis has been described as a 'foundational' method (Braun & Clarke, 2006) suitable as a learning tool for novices in qualitative methodology, the skill required to derive themes salient to the research question surely makes it more than a basic tool. Thematic analysis, as the poor and lesser relative of grounded theory, has no 'kudos' as an analytic method: its flexibility (which allows a number of analytic approaches) and lack of a 'cook-book' on how high-level interpretation should be performed, have earned it the rather unflattering nickname of 'anything goes' qualitative research (Antaki, Billig, Edwards, & Potter, 2003) and result in a reduced interpretative power (Braun & Clarke 2006, p.97). To mitigate this limitation, it was important to adhere to criteria for conducting good qualitative research, which describes how data collection and analysis should be done to achieve internal validity. Seale (1999), Silverman (2000) and Parker (2004) list a set of criteria for assessing quality in qualitative research which relate to transcription, coding, analysis and report writing.

Limitations related to the think-aloud method and the use of vignettes as simulations of real-life case scenarios can also be considered.

Think-aloud has been criticised as a method of generating accurate data, as it may yield potentially inaccurate verbalisations, as the cognitive processes involved in verbalisation are in fact distinct from those involved in generating response to the stimulus (Nisbett & Wilson, 1977). Although technically this is correct, Ericson and Simon (1980)

demonstrated that ‘concurrent’ direct verbalisations (as opposite from retrospective verbalisations, which would be asking participants to recall what they have been thinking when presented with the stimulus and which may be subject to cognitive bias) are in fact consistent and complete representation of the mental process. To mitigate for any shortfalls, the study used the embedded interview process to elucidate some of the statements or reasoning strategies, and challenge inconsistencies or data that looked like it may have been subject to ‘augmentation’ or bias via past learning experiences.

The use of ‘vignettes’ as stimulus instead of a real-life clinical scenario allowed the presentation of a standardised set of information to all participants – but can be said that they are not a complete representation and lack the veracity and fidelity of a real patient. Friedman, Prywes, & Benbassat, (1989) state that nuances that a real presentation gives, from the visual information, to the tone of verbal communication and the array of non-verbal communications, cannot be easliy transcribed into a vignette. Whilst accepting that the use of think kind of stimulus to elicit data is not ideal, its content validity can be a proxy-measure for general validity, if it proivides a robust representtion of a real case (Holzemer & McLaughlin, 1988) – which was the case in this study. Every effort has been made to ensure that the vignettes are representative of the array of symptoms displayed by patients with first episode psychosis, which was indicative of schizoprenia by a display of both positive and negative symptoms and ‘loose’ enough to allow eliciting information on how diagnosis is made (as opposite to presenting a case with a clear-cut diagnosis) as this was postualted to influence clinical-decision making.

The adequacy of data is the next quality indicator that must be considered in a critical review of a study. Erikson (1986) proposes that adequate amounts of evidence, adequate variety in the types of evidence and adequate disconfirming evidence are required. The adequate amount of evidence does not necessarily rely on the number of participants but in

the information-richness of the cases – and the methods section above explains how this was achieved: data was gathered to the point of 'redundancy' i.e no ned information was forthcoming from recruiting further participants. However, the limitations of the study can be linked to the choice of sample. The purposive sampling of clinicians with experience in prescribing for schizophrenia the study was in keeping with the aims and objectives of the study. However, by opportunity sampling from only one Health Board in Wales this sample was limiting in relation to the scope and possibly introduced a bias. This bias relate to the difference in scope of NICE guidelines between England and Wales: in Wales, the following the guidelines is a recommendation, and a good practice point whilst in England there is the added financial incentive: prescribing outside the NICE approved formula will likely generate commissioning issues and the Clinical Commissioning Groups are unlikely to allow it in the service planning or sanction it in the evaluation. This is bound to influence clinician behaviour and therefore it is very likely that some economic considerations would have emerged as factors influencing prescribing. However, at the time of the interviews the NICE guideline allowed the prescribing choice to be made by the clinician therefore the impact of financial factors would have been smaller – but still present as pre-conditioned, learned behaviour. In addition, Heath Boards in Wales produce performance reports which incorporate the cost of prescribing and which are used to assess performance during the appraisal and revalidation process; as such it was expected that this would mitigate the impact of limiting the sample to Wales.

Limiting the sample to one organisation might have also had an impact in terms of organisational culture. We know that from extrinsic factors, organisational culture plays a very important role in how decision-making is shaped and how knowledge translation and implementation happens. However, the heterogeneity of the sample allowed for some mitigation of this drawback. At the time of the interview, the larger Health Board has just

emerged from an organisational change with saw the merger to 3 large individual NHS trusts, each with its own strong organisational culture. Also, the sample included community as well as hospital practitioners which supported further heterogeneity. One limitation remains though in relation to this sample, that related to research expertise: if the sample would have been taken from clinicians employed by a large teaching hospital affiliated to a medical school, it is possible that the discourse relating to research may have been different and research would have featured more prominently.

Last but not least, the 'adequacy of interpretation' as a quality indicator was the one most difficult to achieve. As this is described as a continuous interactive process (Morrow, 2005) it required repeated returns to interviewees for additional data and clarifications to mitigate for the tendency to add my own interpretation to the data. This was not limited to seeking a confirmation of the accuracy of the transcripts but rather clarifications that the meaning of what was recorded was indeed what the participant meant. An immediate disadvantage was that some of the interviews preferer to withdraw from the study, as previously mentioned, amongst concerns that the data as recorded is not an accurate reflection of their practice. I have kept analytic memos on each of the interview which were part of the interpretation process for the data and which supplemented that transcripts - and I set out an analytic framework (Strauss & Corbin, 1009) to integrate the notes and memos in the analysis of the original text - however, some degree of subjectivity is apparent in the writing as hunches, feelings and interpretations from the memos have found their way into the final interpretation of the themes.

The writing and presentation of the themes aimed to strike a balance between the quotes that support and illustrate the theme and my own interpretation of what they may mean - and in a positivist manner the interpretation has been presented in tabular or grahich format to aid

understanding; for example, table 7 and 8 and figure 15 are an illustration of my own interpretation on what the data may mean or how it could be aggregated into a testable hypothesis.

Despite the limitations listed above, the present study provided insight into the main factors supporting variations in prescribing practice, and supports the hypothesis that different types of clinicians will be employing 'tailored' models of EMB by attributing different weight to different contributing factors.

The themes identified in this study map onto factors of the EBM model developed by Haynes et al. (2002), who highlight that *"evidence does not make decisions, people do"* and factors that contribute to the decision-making include *clinical experience* to coordinate and integrate *research evidence* with *clinical state and circumstance* and *patient's values*. Clinical state and circumstances refers to the patient's condition and the circumstances surrounding his/her presentation and or treatment seeking behaviour, as a determinant of patient's individual needs, (such as whether a diagnosis has been made, or whether the patient can access treatment) and 'patient values' reflect their preferences and actions and how strongly those values and beliefs are likely to be in respect of the treatment (as a determinant to adherence to treatment).

The theme exploring confidence and reliance on research findings maps on the '*evidence'* factor of EBM.

The next theme highlighs that the choice of treatment is informed by clinician's views and beliefs in relation to the clinical efficacy and side-effect profile of a particular treatment which form his/her *clinical experience*– which is the EBM factor required to integrate evidence with the particular patient circumstance.

The theme discussing the extent of patient involvement in formulating a treatment plan maps onto the 'patient preferences and actions/patient values' factor of the EBM model and the theme exploring how diagnostic is reached maps on the 'clinical state and circumstance' factor.

In addition to these classic EBM factor, the study has identified themes that may constitute additional factors which come into play in the clinical-decision making process: *normative beliefs* that clinicians hold (from the theme pertaining to scope and value attributed to information), their particular position in relation to *risk management* (from theme 6 discussing perception of risk as a determinant of treatment strategy), and the level of *behavioural control* they feel they have (from the theme exploring the balance between self-efficacy and reliance on others in the decision-making process). A graphical representation of how the themes map onto factors of EMB and new factors identified in the study is presented in Table 7. The codes from which the themes were derived are listed and circumscribed to each factor. For example, the theme "perception of risk is an indicator of treatment choice, and containing risk may take priority over clinical outcomes" emerged from codes such as: 'risk averse', 'concerned with safety', 'risk shared with peers', or 'attuned to risk' and 'takes responsibility'; this theme maps onto the factor identified as Risk Management – and is additional to classic EBM factors.

Figure 15 aims to highlight how the relationship between these factors might be indicative of certain behavioural typologies, distinct 'behavioural profiles' to which each EBM factor contributes something different, either because of its positioning, or due to the weight attributed to it. For example, risk averse participants tended to focus on getting the diagnostic right and prescribing to mitigate side-effects; participants for whom risk did not have a substantial weight tended to focus of immediate action to treat symptoms (rather than a diagnosis) and their main target was efficacy (rather than avoidance of side-effects).

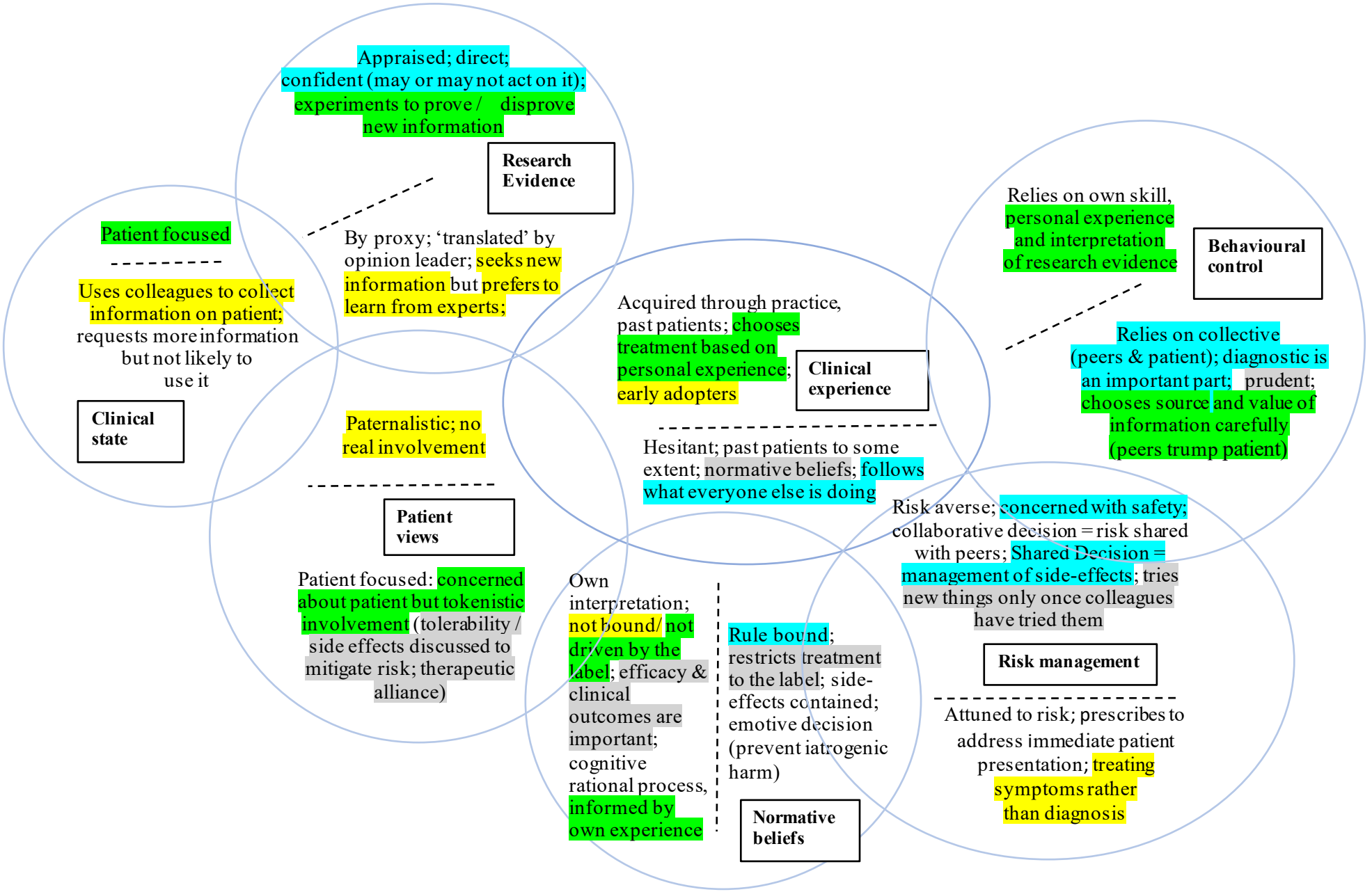
To better illustrate the algorithm of knowledge, experience and beliefs that make up the decision-making process for each ‘behavioural profile’ figure 15 presents the codes that made up this profile in a different colour.

Table 7.

Factors involved in decision making

Theme	Codes from which the themes emerged		EBM factor (+ factors identified in the study)
Ownership and collaboration	Relies on own skill, experience and interpretation of research evidence; uses colleagues to collect information on patient	Relies on collective (peers & patient) to reach agreement; prudent; diagnostic is an important part	Behavioural control
Scope and value attributed to information	Rules/ guidance: own interpretation, not bound by the rule	Rule bound; restricts treatment to label	Normative values and beliefs
Confidence /reliance on research evidence	Appraised; direct; confident; experiments to prove/disprove new information; takes research evidence at face value	By proxy; translated by opinion leader; prefers to learn from experts	Research Evidence
Choice of treatment informed by values and beliefs	Prescribes to address Immediate patient presentation. Typically treating symptoms rather than diagnosis. Experience acquired through practice, chooses treatment based on personal experience	Side-effect risk management; own routine; tries new things only once colleagues have tried them. Experience acquired via past patients; hesitant; normative beliefs; follows what everyone else is doing	Clinical experience
Patient involvement is limited	Paternalistic; no real involvement	Patient focused: concerned about patient but tokenistic involvement (tolerability / side effects discussed to mitigate risk; therapeutic alliance)	Patient views and values
Value ascribed to information is contingent of its source	Information required; ; (clinical picture) Patient's views sought	Colleagues views (clinical picture); Requires more information but not likely to use it; chooses source carefully (peers trump patient);	Clinical state and circumstance
Perception of risk is a good indicator of treatment	Attuned to risk; takes responsibility Efficacy clinical outcomes are important; cognitive rational process, informed by own experience	Risk averse; shared with peers (collaborative decision-making). Patient Shared Decision-making; concerned with safety. Risk management /side-effects contained; emotive decision (prevent iatrogenic harm)	Risk management

Figure 15. Relationship between factors denote specific typologies



The notion of specific "typologies" is not new and has been used by the pharmaceutical industry to derive a marketing segmentation process, based on commonly used behavioural descriptors, so that an appropriate marketing strategy could be devised to target those behaviours. Spielmans (2009) describes this process as employed by Eli Lilly to market off-label prescribing of Zyprexa® (olanzapine) as a treatment for dementia and 'complicated mood' in sub-threshold cases of bipolar disorder and schizophrenia 'lite'. The focus of the marketing message campaign was to address the way in which the drug was prescribed in Primary Care to treat "symptoms and behaviours found in mood, thought, and behavioural disturbances" (Eli Lilly, 2000b). As the drug was licenced for use in schizophrenia but in the main prescribers were not in primary care, Lilly focused its marketing efforts in to expand its treatment market, using the same model it used for fluoxetine. Olanzapine was discussed as a 'broad spectrum psychotropic' which could be used to treat symptoms such as anxiety, irritability, disturbed sleep, mood swings (indicatives of 'complicated mood') and "thought disturbance, including disorganized thinking, as well as poor attention, poor judgment and lack of insight […] socially isolated and poor personal hygiene" (Eli Lilly, undated-e, cited in Spielmans (2009)) - all poorly defined conditions, which would not place the hypothetical patient in a recognized DSM-IV disorder category and not necessarily meeting the clinical cut-off point at which referral to the psychiatrist was required[9].

[9] Interestingly, the only reference to positive symptoms is vaguely centred around disorganised thought, and the rest are negative symptoms. Whilst a more specific reference to positive symptoms would have placed this 'bordeline' patient in a diagnosable category and therefore defeating the goal of market expansion as this would not have been treated in primary care, the focus on negative symptoms is also debateable, as antipsychotics generally are not very successful at treating them.

Two main themes appear in the documents, one being treatment of symptoms (which should appeal to the typology of clinician whose behavioural intention is to treat the symptoms not necessarily a diagnosis) and the other one the ability of primary care to treat 'milder' forms of a condition.

This is relevant because the NICE Clinical Guideline 1 encourages GPs to initiate treatment for acute symptoms of schizophrenia (1.2.3.1), and therefore taking action to address more ambiguous symptoms will not be contrary to the guidelines, which should appeal to the 'rule bound' type of clinician.

A confidential company document (Eli Lilly and Company, 2002) describes the marketing strategy (the Sigma Programme) based on cross-brand segmentation and distinct behavioural patterns identified for each segment. Five different typologies of clinicians were elaborated and were labelled as High-Flyer, Sceptical Experimenters, Selective Majority, Rule Bound and Systematic Conservative.

Four of the profiles described by Lilly match typologies that emerged in the thematic analysis. [10] None of the characteristics of the fifth one, Selective Majority emerged in the themes, and this may be due to the limitations of the study or simply because the characteristics of this typology (diagnosis focused, regular and systematic approach, concern for safety) mapped better on another typology. The other four categories however, were well illustrated by the data (Figure 15) and the themes that emerged showed consistency with patterns of behaviour.

[10] There is no reason to not take into account the high level of expertise and investment that were required to carry out the marketing study and therefore I believe that the typologies identified by Lilly have got the degree of scientific value that can become transferable information, and therefore used in this thesis. Their initial purpose and how these typologies were used by Eli Lilly to achieve their marketing goal is irrelevant for the purpose of this study.

This however, is a theoretical construct - and for it to gain external validity it must become a testable hypothesis. If we look at normative beliefs and subjective norms and the behavioural control that shape behaviours characteristic to each typology it may be possible to construct a testable hypothesis of these typologies that would bridge the gap between the marketing application as developed by Eli Lilly and real value for knowledge translation and implementation framewoks. In effect, if the hypothesis of different typologies identified in the qualitative study could be tested quantitatively (to ensure a certain degree of generalisability) then the information derived from the themes can be used in a knowledge translation strategy that makes better use of the understanding we have on how clinician and patient specific factors impact on decision-making beyond the EBM framework.

As an initial step it was important to map out the codes from which the themes emerged (or components of the themes) onto the different typologies. The data from the qualitative study showing the relationship between factors (Figure 15) indicate that some codes coalesce on pre-defined characteristics of the typologies; to better illustrate this, the data is presented in a tabular format (Table 8)

For example, for the high-flyer typology, the characteristics identified (pre-defined) by Eli Lilly's segmentation study are information seeking behaviours, self-efficacy and seeking deep understanding of how drugs work, stepping out of comfort zone and willingness to try new medicines (and push the envelope with off-label doses and indications), not bound by rules, guidelines or system; treatment plan is symptom driven, with a primary goal of rapid safety and control. From the qualitative study, codes and constituent elements of themes that mirror this behaviour are: seeks new information but prefers to learn from experts, uses colleagues to collect information about the patient; paternalistic, no real patient involvement in decision-making; early adopter, not driven by label; treats symptoms rather than diagnosis and efficacy is more important than side-effects.

Table 8 maps the relevant attributes of each category, in order to establish how best to test them in a quantitative way.

For example, most attributes were either direct attitudes (attitude to risk, stance on efficacy vs side-effects) normative beliefs ('psychiatrist has more experience than the patient', 'it is important to treat symptoms first', etc.) or subjective norms (suggested behaviour viewed as positive by their peers). Participants demonstrated varying degrees of self-efficacy, i.e. an assurance that they can perform to successfully undertake on their own the action required to produce the clinical outcomes.

Previous research has indicated that individual behaviour is strongly influenced by attitudes, normative beliefs, subjective norms, and confidence in own aptitude and skill to perform that behaviour. The Theory of Planned Behaviour (Ajzen, 1991) connects the way in which these elements combine to produce a behavioural intent and ultimately result in a specific behaviour. By mapping the elements identified in the thematic analysis on the TPB model it is possible to construct a questionnaire to test the veracity of the four distinct typological behaviours.

TPB however, is only one such model against which this hypothesis can be tested. Other behavioural change theories may also provide an adequate framework for testing the applicability of the typology and the saliency of the themes identified in the qualitative study in relation to this typology. One such framework might be provided by the Fogg Behaviour Model (FBM) which stipulates that behaviour is shaped by 3 different factors: motivation, ability and triggers. (Fogg, 2009) Motivation is anchored in either social acceptance or in fear of rejection/ negative outcome and people who are motivated by behaviours that increase or preserve their social acceptance will tend to replicate them; ability refers to the self-efficacy perception at performing a target behaviour and triggers as reminders of the desirability of the behaviour. The elements identified in the qualitative study do not however map very well

onto these factors, in particular the trigger factor did not appear explicitly in any of the codes or themes and whilst this model may explain behavioural change or define means to develop behavioural change interventions it does not provide sufficient scope to test the hypothesis that factors which make up the EBM model and some additional normative values and beliefs and behavioural control factors contribute in different proportion to form distinct typologies or patterns of prescribing behaviour.

The Theory of Planned Behaviour model (Ajzen, 1991) provides a robust framework to test this hypothesis and therefore the next chapter aims to investigate if a questionnaire can be constructed using the TPB framework to test the reliability of factors identified in the thematic analysis as main contributors to prescribing behaviours.

Table 8

Codes or components of the themes identified in the thematic analysis map out on specific typologies

Segmentation /typology	Characteristics as described in the segmentation study (Eli Lilly, 2000a)	Codes /themes from the TAnDeMS study
High-Flyer "I eagerly seek out new ways to treat my patients"	*Seeks new information that will treat more patients, better *Seeks deep understanding of how drugs work; make decisions based on MoA *Likes to have treatment options; tailoring a medication *Stepping out of comfort zone; willing to try new medicines; will push the envelope with off-label doses and indications *Not bound by rules, guidelines or system; proactively take action to get patient better *Symptom driven, with a primary goal of rapid safety and control *Early Adopters	Seeks new information but prefers to learn from experts; Uses colleagues to collect information about the patient; Paternalistic, no real patient involvement in decision-making; Early adopter; Treating symptoms rather than diagnosis; Not driven by label; Efficacy is more important than side-effects
Sceptical Experimenter "I decide how to use medications based on personal experiences / experiences of physicians I respect"	*Tailors therapy to the patient * In control of treatment; does not follow indication s *High expertise in the population *Not bound by rules/guidelines *Not bound by diagnosis *Will push the envelope with off-label doses and indications *Tries new medication to prove or disprove data	Patient focused; Chooses treatment based on personal experience; Experience gets challenged or reinforced; Not rule bound; Chooses source of information and value very carefully; Concerned about patient but tokenistic involvement
Rule Bound "I follow the rules when treating my patients; if you don't follow the rules, you'll pay for it later"	*Wait to use medications when well established in the system *Follow the formulary guidelines *Follows rules dictated by patient type * Diagnosis clearly determined for treatment *Very knowledgeable but don't necessarily act on it *Pressed for time *Moderate Adopters	Knowledge acquired directly (may or may not act on it); Tries new things only once colleagues have tried them; Restricts treatment to the label; Normative beliefs; Follows guidelines and formulary indications; Diagnostic is an important part; Relies on collective (peers and patient) to reach a decision collaboratively; Concerned with safety; risk averse
Systematic Conservative "I have a treatment "system"	*Regular, systematic approach: *Diagnosis/Indication focused, *On label use *Concerned with safety	Confident in own method; Clinical experience acquired through practice, past patients reinforce beliefs; Requests more information but does not act on it. Tries new things only when tested/well established; Restricts treatment to the label; Efficacy and clinical outcomes are important; Tolerability, side-effects discussed to mitigate risk; Therapeutic alliance is important

CHAPTER IV.

Using TheorY of Planned Behaviour to test the PrEvalence of specific factors in ClinicAl decision-making in the treatment of Schizophrenia: the TYPECASt pilot study

The Theory of Planned Behaviour was developed by Ajzen (1991) and explains how behaviour can be predicted by elements that influence it and account for variability in outcome: attitudes about the behaviour, subjective norms, and beliefs about the control on the behaviour (perceived behavioural control) are independent determinants of intention, and cognitive self-regulation plays an important part.

Attitude toward the behaviour refers to the degree to which the actor views the specific behaviour as desirable or not. Subjective norms refer to the perceived social pressure to perform this behaviour. Perceived behavioural control refers to the perceived ease or difficulty of performing the behaviour.

The relative weight of attitude, subjective norm, and perceived behavioural control in predicting the behavioural intention will vary across different behaviours and distinct situations. The principle of aggregation adds the assumption that any single behavioural outcome reflects the influence of various factors particular to the situation which required action, and the general disposition of the actor. In the case of decision-making in schizophrenia, the factors particular to the situation are the patient related factors, such as clinical presentation and circumstance, and patient preferences. Ajzen (1991) clarifies that past behaviours are not a good predictor of future behaviour, due to the variability of the above situational factors. Their contribution (weight) also tends to differ on different occasions (clinical presentation in our case is one of the main contributors to the weight attributed). Nevertheless, having successfully deployed the behaviour in a past similar situation generates a behavioural disposition (clinical experience in our case) *"which the*

individual carries about him from one situation to another" (Atkinson, 1964, p. 242) and this achievement motivation combines with the current situational expectation of success to form an "incentive value".

As in the original Theory of Reasoned Action (Fishbein, 1975) which was the precursor of the Theory of Planned Behaviour, the individual's intention or motivation to perform a given behaviour serves as an indicator of the effort the actor is willing to put into materialising that behaviour. Ajzen explains that, *"as a general rule, the stronger the intention to engage in a behaviour, the more likely should be its performance"* – if this behaviour is voluntary and the actor has the liberty to decide whether to perform the behaviour or not. Although it can be argued that the prescribing behaviour will meet this requirement, acting out on the intent depends also on non-motivational factors, such as skills and cooperation of others. Collectively, these factors represent actual control over the behaviour - and therefore the behaviour will be the resultant of the intent *and* the ability.

The Theory of Planned Behaviour also states that beliefs have an important role to play across the three determinants of behaviour, and ultimately the behaviour is a "function" of salient beliefs that the individual holds.

Three kinds of salient beliefs are described: *behavioural beliefs*, which will shape the attitudes toward the behaviour, *normative beliefs* which will form the substrate of subjective norms, and *control beliefs* as the basis for the perception of behavioural control. Accordingly, Attitude toward the behaviour has two components: *beliefs about the outcome* of the behaviour (prescribing this antipsychotic is likely to reduce symptoms / prescribing this antipsychotic is likely to generate adverse side-effects) and the *outcome evaluations*:

positive or negative judgment about how desirable this is (reducing symptoms is important / side-effects are undesirable)

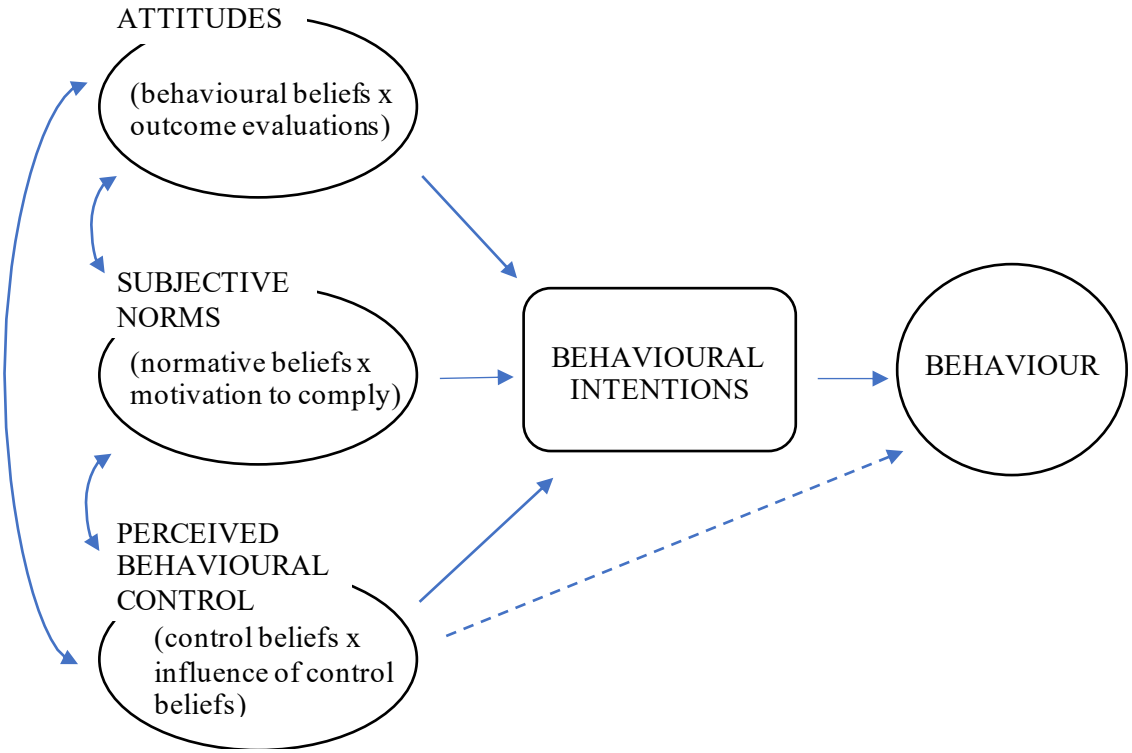
Subjective Norms are a representation of the individual's perception of social pressure to perform that behaviour, i.e. meaningful influencers and peers would approve or disapprove of prescribing this particular antipsychotic. This too has two components: the beliefs about how these peers would want the individual to behave, the *normative beliefs* (I feel pressure from the patient for prescribe this drug/ Senior Consultant on my ward prescribes this) and the individual's *motivation to comply* with the social pressure (doing what patients think I should do is important to me/ the Professor would disagree if I were to prescribe another drug)

Perceived Behavioural control is a representation of the ability to enact the behaviour (I can prescribe this antipsychotic) and its two components are the *control beliefs* (individual's perception of control over the behaviour, e.g. I can prescribe what I see fit for this patient vs. I'd like to discuss this with the consultant/the team) and the *confidence on being able to act* – i.e. the power of/over situational/internal factors to facilitate/obstruct the behaviour (e.g. consultant/pharmacist may override me)

Thus, beliefs about the consequences of a behaviour will determine the Attitudes towards that behaviour, normative beliefs will determine Subjective Norms, and control beliefs about are underlying Perceived Behavioural Control (Figure 16)

Figure 16.

Theory of Planned Behaviour



Source: From: Ajzen, I. (1991). *The Theory of Planned Behavior*. Organizational Behavior And Human Decision Processes (vol 50, issue 2 pp. 179-211) https://doi.org/10.1016/0749-5978(91)90020-T Copyright © 1991 Elsevier Inc. – with permission

This can be expressed as a mathematical function:

$\mathbf{B=w_{BI}BI+w_{PBC}PBC}$ where $\mathbf{BI=(w_A)A+(w_{SN})SN+(w_{PBC})PBC}$

In this equation, **BI** is the Behavioural Intention and

attitude toward behaviour (**A**) is directly proportional to the summative belief index (**b**) the strength of each belief, and (**e**) the subjective evaluation of the outcome, across each attitude

($_i$) salient to a particular situation: $A \propto \sum b_i e_i$.

The Subjective Norm (**SN)** is directly proportional to the sum of resulting products between (**n**) the strength of the normative belief multiplied by (**m**) the motivation to comply with a particular "referent" - across multiple referents $SN \propto \sum n_i m_i$

Perceived Behavioural Control (**PBC**) is directly proportional to the resulting products of (c): the strength of each control belief multiplied by (p): the perceived power of the control factor to facilitate/obstruct the behaviour - summed across n salient control beliefs. $PBX \propto \sum c_i p_i$

(w) is an empirically derived weight coefficient (Ajzen, 1991)

Research question

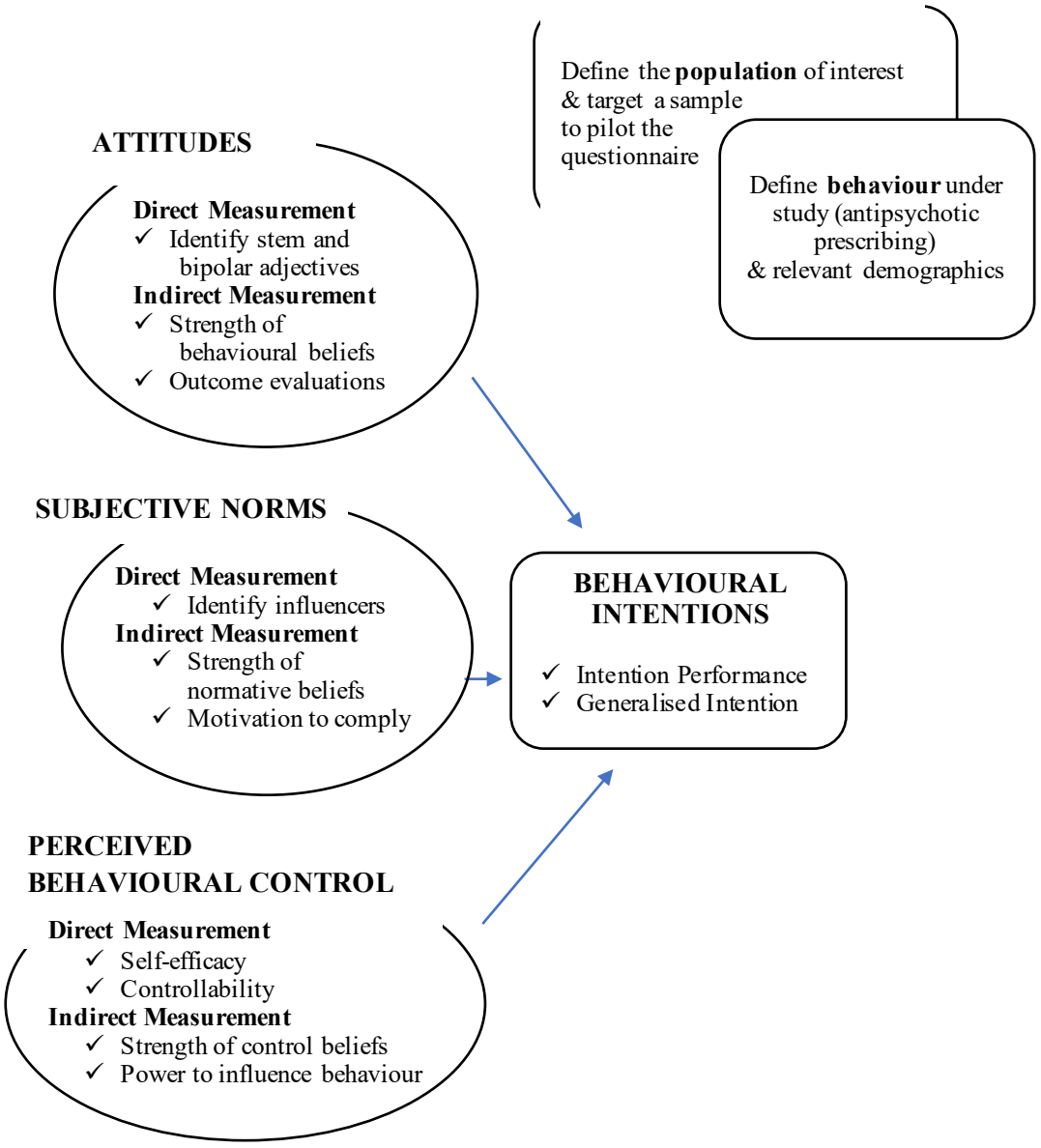
The study aims to identify - as proof of concept - whether it is possible to use this framework to identify a positive correlation between attitude toward antipsychotic prescribing, subjective norms related to antipsychotic prescribing, perceived behavioural control influencing antipsychotic prescribing and behavioural intention – and whether these vary with clinician characteristics (clinical experience, gender, position in the team, level of responsibility) and could map onto different typologies identified in the thematic analysis. This is a feasibility study, not an evaluation, rather aiming to answer the 'can we' and the 'what if' questions. To this end, the objective is to use the factors identified in the thematic analysis to construct a questionnaire based on the TPB framework and to establish whether the items have validity and reliability required. A valid and reliable questionnaire could be used to determine whether attitudes, subjective norms or perceived behavioural control influence behavioural intention in different proportions for different groups of people.

Constructing the Questionnaire

The Manual for Constructing Questionnaires based on the Theory of Planned Behaviour (Francis et al., 2004) describes nine steps required to identify salient components. (Figure 17).

Figure 17.

Constructing a questionnaire based on the Theory of Planned Behaviour framework



Source: adapted from Francis, J. J., Eccles, M. P., Johnston, M., Walker, A., Grimshaw, J., Foy, R., … Kaner, E. (2004). *Constructing Questionnaires Based On The Theory Of Planned Behaviour A Manual For Health Services Researchers.* Centre for Health Services Research, University of Newcastle upon Tyne, http://openaccess.city.ac.uk/1735/, © University of Newcastle upon Tyne, 2004 – CC-NC.

All the prerequisites to construct the first draft of the questionnaire (defining the population and the behaviour under study) were derived from the TAnDeMS study.

The population of interest was limited to psychiatrists with experience in prescribing for schizophrenia (i.e. child and adolescent psychiatrists and old age psychiatrists were only eligible to take part if their experience with antipsychotics extended to schizophrenia and not only to their use as mood stabilisers). The selection of a representative sample has taken into account that the first stage is to validate the questionnaire as a construct (proof of concept) and establish internal consistency with the themes derived from the qualitative study; therefore, the participants in the TAnDeMS study have been approached initially. An additional random sample was then invited to take part: psychiatrists from the same Health Board in Wales, as well as elsewhere in the UK completed the pilot version of the questionnaire.

The behaviour under study was limited to prescribing a specific antipsychotic, incorporating all the elements that lead to the prescribing decision.

Measuring Behavioural Intention

Francis et al. (2004) describe that this measurement could be elicited in different ways, either as *intention performance* ("Given 10 patients presenting with schizophrenia, how many patients would you expect to prescribed drug x to?), as a *generalised intention* ("I expect to prescribe drug x to patients with schizophrenia: Strongly disagree /…/ Strongly agree) or as an *intention simulation* (in which a scenario of a hypothetical patient is presented in a 80-100 words vignette and the decision to prescribe drug x is elicited as a yes/no option). For the purpose of this study the third option would have been unsuitable, as the thematic analysis already highlighted that clinicians need a lot of additional information to about a 'hypothetical patient' to reach a decision and this would act as a significant cofounding factor

in eliciting behavioural intention, but the intention statements that emerged in the study were used to define the parameters for measuring intention performance and generalised intention. Furthermore, one of the main considerations was that that given that engrained familiarity with the DSM-IV categorisation most clinicians might differentiate mentally between various sub-types of schizophrenia and this would then act a barrier to an intuitive 'system 1' reaction which the questionnaire could capture. To mitigate for this the questionnaire used "a typical presentation of schizophrenia" as an expression to direct a generalised intention, and the intention simulation used in the thematic analysis was used to derive the factors used in the construct. For internal consistency, three constructs were used: "I expect to prescribe an atypical antipsychotic for each patient with a typical presentation of schizophrenia" , "I want to prescribe an atypical antipsychotic (etc)" and "I intend to prescribe (etc)" - and although empirically there is a high degree of consistency between responses, Armitage and Conner (2001) highlight that the three items are conceptually distinct. In the thematic analysis study, the expression "I want to" and "I expect to" appear more often as a self-reported behavioural intent. "I intend to" only appears once in this context, but "I would (etc)" appears as a suitable substitution.

Intention performance scored on a continuum from 0 to 10. All three constructs in the generalised intention were scored on a continuum from 1 to 7 from Strongly Disagree to Strongly Agree (Table 9). The mean of the 3 intention scores gives the final score for behavioural intention.

Table 9.

Measuring Behavioural Intention

Intention performance										
Q: Out of the next 10 patients you see with a diagnosis of schizophrenia, for how many patients you expect to prescribe an atypical antipsychotic										
Scoring:	1	2	3	4	5	6	7	8	9	10
and										
Generalised intention										
I expect to prescribe an typical antipsychotic for each patient with a diagnosis of schizophrenia										
Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree		
I want to prescribe an atypical antipsychotic for my patients with schizophrenia										
Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree		
I intend to prescribe an atypical antipsychotic to patients with a presentation of schizophrenia										
Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree		

The manual then directs to determine how best to measure *the attitudes*: the 'most frequently perceived advantages and disadvantages in performing the behaviour', *the subjective norms*: who are the influencers who would 'approve or disapprove of the behaviour', and the *perceived behavioural control*: barriers and facilitators that influence the ability to 'adopt the behaviour' – and include all these items into constructs that can be piloted and amended to stand up to test-retest reliability.

In order to determine which factors identified in the thematic analysis mapped onto the constructs of the questionnaire, it was necessary to identify which of the factors were self-defined as attitudes (and behavioural beliefs), subjective norms (and normative beliefs) or perceived behavioural control (and control beliefs respectively).

Measuring Attitudes

The TPB questionnaire construction manual requires a direct and an indirect measurement. For the direct measurement, the construct needs to identify polar opposite evaluative adjectives, such as 'good/bad' and instrumental (the behaviour achieves something) and/or experiential (how it feels to perform the behaviour). For the purpose of the study 'desirable/undesirable', 'safe/unsafe', 'efficacious/inefficacious', 'evidence-based/bad practice' and 'right thing to do/wrong thing to do' were used, on a 1 to 7 continuum – with the attributes arranged so that the ends of the scale were a mix of positive/negative connotations to minimise the 'response set'. It is recommended to use four items following a single "stem" which defines the behaviour, and in this case "Overall, I think prescribing an atypical antipsychotic is (etc)" was used as a stem. The aim of this construct is to assess the perspective of the actor, not the implication of the behaviour for the patient, as this would classify better a control belief not a measurement of attitude. The mean of the item scores gives the overall attitude item score. A correction is applied to reverse score /recode the negatively worded endpoints so that higher numbers always denote a positive attitude towards the prescribing behaviour; for example, a 6 will become a 2 when a correction is applied.

For the indirect measurement, the manual requires to identify commonly held beliefs to construct items that assess the strength of the behavioural belief and the outcome evaluation– and these came from terms that appeared in the thematic analysis. These were behavioural beliefs linked to safety and efficacy profile of the drug, such as "I am doing something positive for the patient', "Weight gain causes a lot of worry and concern for the patient", "If I prescribe an atypical I will reduce positive symptoms at an early stage". To assess outcome evaluations each of the belief statements was converted to an 'incomplete sentence', enabling the respondent to carry out a positive or negative evaluation of the belief statement (Table 10).

Table 10.

Measuring Attitudes

Direct measurement								
I think that prescribing an atypical antipsychotic to patients with schizophrenia is								
	Unsafe	1	2	3	4	5	6	7	Safe
	Effective	1	2	3	4	5	6	7	Ineffective
The wrong thing to do	1	2	3	4	5	6	7	The right thing to do
Evidence-based	1	2	3	4	5	6	7	Bad practice
Indirect measurement								
Behavioural beliefs								
If I prescribe an atypical antipsychotic I feel I am doing something positive for the patient								
	Unlikely	1	2	3	4	5	6	7	Likely
Weight gain causes a lot of worry to the patient								
	Unlikely	1	2	3	4	5	6	7	Likely
If I prescribe an atypical antipsychotic I will reduce positive symptoms at an early stage								
	Unlikely	1	2	3	4	5	6	7	Likely
If I prescribe an atypical antipsychotic I get to see if the drug works								
	Unlikely	1	2	3	4	5	6	7	Likely
Outcome evaluations								
Doing something positive for the patient is:								
	Unimportant	-3	-2	-1	0	1	2	3	Important[11]
Worries and concerns expressed by patients treated with atypical antipsychotics are								
	Undesirable	-3	-2	-1	0	1	2	3	Desirable[12]

[11] The Francis et al. (2004 p.15) manual advised that should some statements "seem downright silly", such as 'Doing something positive or the patient is important/unimportant', if the pilot study returns a zero variance, the final version can omit these statements and replace the score for a behavioural belief with a constant "selected intelligently by the researcher". For the purpose of this study, the question has been left in as the thematic analysis indicated that not all clinicians would want to act in accordance to patient's preferences and this statement could act as behavioural differentiator.

[12] This item has a semantically different evaluator , where 'important/unimportant' has been replaced with 'desirable/undesirable', as the thematic analysis highlighted that clinicians believe that patients who expressed worry about their condition or treatment are more likely to be treatment compliant. Moreover, most clinicians will have a discussion about worries and concerns with the patient, and the item will measure how desirable is that patients initiate this discussion or are able/willing to discuss.

Reducing positive symptoms at an early stage is:

	Unimportant	-3	-2	-1	0	1	2	3	Important

Seeing for myself if a drug works is:

	Unimportant	-3	-2	-1	0	1	2	3	Desirable

The overall attitude score is the sum of all products across behavioural beliefs: for each belief, the score on the likely/unlikely score is multiplied by the evaluation score on the desirable/undesirable score.

A= (**a** x **e**) + (**b** x **f**) + (**c** x **g**) + (**d** x **h**), where a, b, c and d are scores for each of the behavioural beliefs and e, f, g and h the outcome evaluations for each behavioural belief.

A positive score means that the respondent is in favour of prescribing an atypical antipsychotic, and conversely, a negative score means that that the respondent is against prescribing an atypical antipsychotic. The behavioural beliefs are measured unidirectionally (on a unipolar scale from 1 to 7, whilst outcome evaluations are measured bidirectional, on a bipolar scale from -3 to 3 - as the concept to be measured is either the probability or an evaluation.

As there are 4 items on this scale, the range of possible total scores is 4 x (7 x ±3) = -84 to 84, and the differences in range between predictor variables are suitable for correlational analysis. The mean of multiplied scores measure absolute values of predictor variables within the item A= (7 x ±3).

Measuring Subjective Norms

As with measuring Attitudes, measuring Subjective Norms entails a direct and an indirect measurement. The direct measurement involves questions related to opinions of influencers. As the thematic analysis identified a *range of influencers*, this item does not have a specifically named person but rather refers to influencers as ‘people who are important to me’ and the detailed descriptors were used in the indirect measurements (‘other psychiatrists’,

'NICE', 'patients'). The format is a complete statement and the scoring is on a unidirectional scale from 1 to 7 from 'Strongly disagree' to 'Strongly agree'. The mean of the item scores is the overall subjective norm score.

The indirect measurement uses the same commonly held beliefs identified in the thematic analysis (elicitation study) and labels of sources of social pressure; the items assessing the strength of the normative beliefs coverts these sources into 'stems' of normative belief items which reflect what influencers do or what they think the respondent should do. The strength of motivation to comply is measured by converting each of the sources of social pressure into a statement about its importance to the respondent (Table 11)

For Direct measurements the mean of the items scores gives the overall subjective norm score. For Indirect measurements, the belief score is multiples by the motivation score; the overall subjective norm score is the summed products across all the beliefs:

N= (**a** x **e**) + (**b** x **f**) + (**c** x **g**) + (**d** x **h**), where a, b, c and d are scores for each of the 4 normative beliefs and e, f, g and h are scores for the motivation to comply with each source of social pressure.

Table 11.

Measuring Subjective Norms

Direct measurement								
People that are important to me think that I should not prescribe atypical antipsychotics								
	Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree
I feel under social pressure to prescribe atypical antipsychotics								
	Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree
It is expected of me to prescribe atypical antipsychotics								
	Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree

Indirect measurement							
Strength of normative beliefs							
My experience tells me that I ….							
	should not	-3	-2	-1	0	1	2	3	should
				prescribe atypical antipsychotics					

Patients with schizophrenia …

disapprove -3 -2 -1 0 1 2 3 approve
of my prescribing atypical antipsychotics to them

Other psychiatrists …

do not -3 -2 -1 0 1 2 3 do
prescribe atypical antipsychotics to patients with schizophrenia

NICE would …

disapprove -3 -2 -1 0 1 2 3 approve
of my prescribing atypical antipsychotics to patients with schizophrenia

Motivation to comply

Doing what other psychiatrists do is important to me:

Not at all 1 2 3 4 5 6 7 Very much

Following my own experience is important to me

Not at all 1 2 3 4 5 6 7 Very much

Following NICE guidelines matters to me

Not at all 1 2 3 4 5 6 7 Very much

The approval of my patients is important to me

Not at all 1 2 3 4 5 6 7 Very much

A positive score means that the respondent experiences social pressure to prescribe atypical antipsychotics for patients with schizophrenia, whist a negative score means that the respondent feels social pressure not to prescribe. The possible range of total scores is -84 to +84.

Measuring Perceived Behavioural Control

Direct measurements of perceived behavioural control rely on items that measure self-efficacy (the respondent confidence that they are capable of performing the target behaviour) and their beliefs about the controllability of that behaviour. Self-efficacy is measured by the difficulty of performing the behaviour and the respondents' confidence that they can do it, and controllability is measured by establishing whether respondents believe prescribing is up to them or there are extrinsic factors that determine the behaviour. The format is incomplete

sentences and the scoring is on a scale from 1 to 7 with mixed positive and negative endpoints.

The indirect measures revolve around the content of the commonly shared control beliefs identified in the elicitation study (thematic analysis) and the questionnaire assesses the strength of these control beliefs that may make it difficult to prescribe (or not prescribe) atypical antipsychotics - and the power of the control factors for influence the behaviour. For example, in Wales, medicines rejected for use by NICE or by the Wales Medicines Strategy Group are placed on a 'Blue List'. Those drugs have been considered by the Drugs and Therapeutics Group who have agreed that they should not be prescribed by either consultants or GPs in Wales. Paliperidone is on the current blue list and prescribing requests for paliperidone lengthen some consultations and create a degree of prescribing administration which had been identified as a perceived behavioural control factor.

The items assessing the strength of control beliefs convert the factors identified by clinicians into a set of statements, scored on a scale from 1 to 7 and the power of these factors to influence the behaviour is assessed by incomplete statements about whether this makes it more or less likely that they will prescribe atypical antipsychotics and whether it makes it more or less difficult to do so (Table 12)

The scoring of direct measurements requires recoding of negative endpoint on the right, so that high scores consistently represent a greater level of control; the mean item of the scores gives and overall perceived behavioural control score. For indirect measures, the belief score is multiplies by the power of control score of the same item and the resulting products are summed across all items: **PBC**= (**a** x **e**) + (**b** x **f**) + (**c** x **g**) + (**d** x **h**), where a, b, c and d are scores for each of the 4 control beliefs and e, f, g and h are scores for the power of control. A positive score means that the respondent feels in control over prescribing behaviour, and conversely, a negative score means the respondent does not feel in control.

Table 12.

Measuring Perceived Behavioural Control

Direct measurement								
Self-efficacy								
I am confident that I can prescribe atypical antipsychotics if I want to								
Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree
Prescribing atypical antipsychotics is …								
easy	1	2	3	4	5	6	7	difficult
Controllability								
Whether I prescribe atypical antipsychotics is entirely up to me								
Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree
Indirect measurement								
Strength of control beliefs								
Atypical antipsychotics are not very effective								
Unlikely	1	2	3	4	5	6	7	Likely
I feel rushed into making a decision								
Unlikely	1	2	3	4	5	6	7	Likely
The side-effects of atypical antipsychotics are uncomfortable for patients								
Unlikely	1	2	3	4	5	6	7	Likely
I need more information from the patient before I prescribe an atypical antipsychotic								
Unlikely	1	2	3	4	5	6	7	Likely
Power of control factor (influencer)								
I am …								
less likely	-3	-2	-1	0	1	2	3	more likely
to prescribe atypical antipsychotics if they are effective								
I am ….								
less likely	-3	-2	-1	0	1	2	3	more likely
to prescribe atypical antipsychotics if they have side-effects								
I am ….								
less likely	-3	-2	-1	0	1	2	3	more likely
to prescribe atypical antipsychotics if I feel rushed into making a decision								
I am ….								
less likely	-3	-2	-1	0	1	2	3	more likely
to prescribe atypical antipsychotics if I need more information about the patient								

In summary, the construction of the questionnaire used factors identified in the thematic analysis (TAnDeMS study) as an elicitation phase to identify items that best describe attitudes towards antipsychotic prescribing, (including behavioural beliefs, such as perceived advantages and disadvantages / views on research evidence, attitude towards risk - and outcome evaluations, i.e. the weight these beliefs carry), subjective norms (including normative beliefs, such as views of influencers, people or groups who would approve or disapprove of their prescribing behaviour - and motivation to comply with the normative beliefs) and establish factors that define perceived behavioural control (including control beliefs, such as ability to prescribe being dependent on budget issues, formulary issues or administrative burden - and the perceived power of influences over the prescribing behaviour).

The first version of the questionnaire contained 87 preliminary items and was piloted on a small sample (11 participants, with a view to evaluate acceptability and feasibility and refine it accordingly. The distribution of responses for each item was assessed: items that showed little validity were removed or replaced. Some items were reworded, for example, all questions that listed ‘atypical antipsychotic’ were replaced with ‘the antipsychotic of your choice’ and the questionnaire had an additional item in the demographic section to ascertain which 2 or 3 drugs participants would prescribe routinely for schizophrenia. This increased the internal consistency as it removed the confounding potential of guiding the participant to think about all atypical rather than about the drugs they would prescribe. A number of items were removed entirely as they were duplicative or ambiguous - and the length of the questionnaire was reduced to 41 items, for conceptual reasons (as a greater number of items would artificially increase the value of Cronbach’s Alpha as reliability measure), as well as

practical considerations (as a shorter version should require less time to complete and would attract more respondents).

A summary of the items across components, scales, the format and scoring key is presented below (Table 13) and the re-worded version of the questionnaire (Appendix G) was distributed in both paper and electronic format. Data from 27 respondents was analysed to determine validity and reliability of items.

Data Collection

The paper format of the questionnaire accompanied by a Participant Information Sheet (Appendix F) was distributed in pdf format attached to a cover-letter email to potential participants. This was disseminated to Mental Health teams within Health Boards in Wales and the Royal College of Psychiatrists, courtesy of RCPsychWales. The email also contained a link to the online version of the survey hosted by JISC Online Surveys, (formerly Bristol Online Surveys) https://bangor.onlinesurveys.ac.uk/questionnaire. This is a secure web-hosted survey facility to which Bangor University is a subscriber, and enables to develop and deploy a survey. The platform has a facility for rudimentary data analysis but this was not used – all data was exported to SPSS instead.

No explicit consent was taken at this time, completion of the questionnaire was deemed to constitute implicit consent. The study was approved by the Research Ethics and Governance Committee in the School of Psychology, Bangor University. No NHS REC approval was required as the study falls outside the scope of GAfREC (does not recruit NHS patients). Given the time-frame restriction imposed by the scope of the PhD, data form the first 27 respondents (online and paper format) was included in the validity and reliability analysis.

Table 13.

Scoring key for the TPB questionnaire

Construct	Measure	Concepts	Question	Response format	Reverse scoring	Item Scoring
Behavioural Intention	Intention statement	Clinical experience; prescribing to symptoms or diagnostic	41	0 to 10		Marked score
	Generalised intention		33,38, 40	1 to 7	33	(33+38+40)/3
Attitudes	Direct measure	Research evidence, attitude to risk, safety vs. efficacy	17, 20 to 23	1 to 7	21, 23	Mean (17,20,21,22,23)
	Behavioural beliefs		1 to 4	1 to 7		(1x11)+(2x10)+ (3x12)+(4x9)
	Outcome evaluations		9 to 12	-3 to +3		
Subjective Norms	Direct measure	Information seeking, label adherence, patient involvement, guideline compliance	18,32, 34,39	1 to 7	32	Mean (18,32,34,39)
	Normative beliefs		13 to 16	-3 to +3		(13x25)+(14x27) +
	Motivation to comply		24 to 27	1 to 7		(15x24)+(16x26)
Perceived Behavioural Control	Direct measure	Ownership and collaboration, organisational factors, peer-pressure / influencers; adherence to rules	19, 35 to 37	1 to 7	37	Mean (19,35,36,37)
	Control belief		5 to 8	1 to 7		(5x28)+(6x30)+(7 x29)+(8x31)
	Power of control factor		28 to 31	-3 to +3		

Source: adapted from Francis, J. J., Eccles, M. P., Johnston, M., Walker, A., Grimshaw, J., Foy, R., … Kaner, E. (2004). *Constructing Questionnaires Based On The Theory Of Planned Behaviour A Manual For Health Services Researchers.* Centre for Health Services Research, University of Newcastle upon Tyne, http://openaccess.city.ac.uk/1735/, © University of Newcastle upon Tyne, 2004 – CC-NC

Results

The aims of the study were to establish whether the items identified in the thematic analysis can be tested using a TPB framework questionnaire, and whether this can be a valid and reliable measure to assess the proportion in which attitudes, subjective norms and perceived behavioural control differ in different groups of respondents.

Data was exported from the Online Survey web platform to Microsoft Excel (the only available export option) and data from paper versions responses was added manually. Variables were defined and labelled and imported in SPSS as a new dataset (IBM SPSS v. 25, 2018).

The demographic characteristics of the sample were analysed using descriptive statistics. Participants responded to these items by selecting the values on nominal scales: number of years they qualified as a psychiatrist (from 3 possible ranges: 1-5, 6-10 and over 10) and current status (Training Grade, Mid-grade, Consultant) as well as gender (male/female). Some additional questions in the questionnaire (list size, sessions worked and number of psychiatrists in the hospital) were not analysed in this study, they were introduced with a view to study at a later date possible correlations with institutional factors. From question eliciting the list of 2-3 drugs they most often prescribe for schizophrenia, variable were labelled “typical” and “atypical” and its use scored 1 /not used was scored 0 on a nominal scale.

The characteristics of the sample are presented in Table 14.

Table 14.

Demographic characteristics of the sample used to establish validity and reliability of questionnaire items in the TYPECASt study

Demographics

		Statistics				
		How long have you been qualified as a psychiatrist?	Gender	Status	Used atypical drugs	Used typical drugs
N	Valid	27	27	27	26	26
	Missing	0	0	0	1	1

Frequency Table
How long have you been qualified as a psychiatrist?

		Frequency	Percent	Valid Percent	Cumulative %
Valid	1-5 years	7	25.9	25.9	25.9
	6-10 years	8	29.6	29.6	55.6
	10+ years	12	44.4	44.4	100.0
	Total	27	100.0	100.0	

Gender

		Frequency	Percent	Valid Percent	Cumulative %
Valid	Male	22	81.5	81.5	81.5
	Female	5	18.5	18.5	100.0
	Total	27	100.0	100.0	

Status

		Frequency	Percent	Valid Percent	Cumulative %
Valid	Training grade	8	29.6	29.6	29.6
	Mid grade	3	11.1	11.1	40.7
	Consultant	16	59.3	59.3	100.0
	Total	27	100.0	100.0	

Used atypical drugs

		Frequency	Percent	Valid Percent	Cumulative %
Valid	Yes	26	96.3	100.0	100.0
Missing	System	1	3.7		
Total		27	100.0		

Used typical drugs

		Frequency	Percent	Valid Percent	Cumulative %
Valid	No typical drug used	19	70.4	73.1	73.1
	Typical drug used	7	25.9	26.9	100.0
	Total	26	96.3	100.0	
Missing	System	1	3.7		
Total		27	100.0		

Parametric tests were used for data analysis as there is no reason to assume that data would not have a normal distribution. Data is fairly symmetrical, with skewness between -0.5 and 0.5 for most items, and moderate skewness for PBC. Kurtosis is also close to 0 for most items, with only one leptokurtic item (intention statement /Q41) which corrected when Rankit's transformation was applied. (Appendix H) . It must be noted however that both skewness and kurtosis are affected by sample size, but in this case we took the approach recommended by Miles & Shevlin (2006) that if the value of skew or kurtosis is greater that twice the standard error it can be assumed that the distribution will differ significantly from normal distribution, and parametric test would be appropriate for an exploratory development.

The first step was to evaluate the validity of each item within the direct and indirect measures. Cronbach's Alpha coefficient was used to assess the internal consistency of direct measures, and Pearson's correlations between direct and indirect measures of the same item were used to confirm the convergent validity and whether indirect measures are well constructed.. [13] The distribution of responses for each item was assesses, and as all variables are ordinal, a polytomous graded response model was used to analyse the validity of items within the construct.

Table 15 summarises the descriptive statistics of participant's responses to the direct and indirect measures. Mean scores for direct measures were just above mid-scale for attitudes, subjective norms and perceived behavioural control - and close to top of the scale for the intention statement. This suggests that respondents considered prescribing the antipsychotic of their choice a worthwhile behaviour, and indicated that their preferred course of action would be to prescribe it for most of their patients with a diagnosis of schizophrenia, but

[13] Cronbach's Alpha is only an appropriate test statistic for direct measures of attitude, subjective norms and perceived behavioural control. Indirect measures are formative indicators of the construct rather than reflective.

looked for endorsement from their peers and exercised only a moderate degree of control over the prescribing behaviour.

Table 15.

Descriptive statistics of participant's responses to the direct and indirect measures

Direct Measures	Items	Mean	Standard deviation	Minimum Score	Maximum Score
Attitudes	5	5.73	0.74	4.2	6.8
Subjective norms	4	4.32	0.81	2.5	5.75
PBC	4	5.61	0.76	3.75	6.75
Intention	1	8.44	1.82	1	10
Indirect measures					
Attitudes	8	45.77	17.24	17	78
Subjective norms	8	51.22	16.82	9	75
PBC	8	-3.92	17.50	-51	28
Intention	3	5.66	1.24	3	7

For indirect measures, mean scores reflect an overall moderately positive attitude (cautious attitude) towards the prescribing behaviour, with some pressure to perform the prescribing behaviour and very low control over the behaviour. There is a degree of discordance in these items which has been explored by identifying measures of reliability for each of the measures. As described above, the internal consistency of *attitudes, subjective norms and perceived behavioural control* was assessed using Cronbach's Alpha coefficient and the reliability of indirect measure was assessed by looking at correlations between the direct and indirect measures within the same construct. Ajzen, (2006) sets an acceptable level of α at >.60, and only *attitudes* satisfied this criterion (.683). Substantive norms yielded a negative value (-.044) which violates the reliability model assumptions as it indicates a negative average covariance between items. This may have been due to an error in coding item 18 which given the semantic double negative should have been reverse coded. Item 18 reads "I feel under pressure to not prescribe expensive drugs" and the scale was coded 1 to 7 strongly disagree to strongly agree – meaning that agreeing with the statement means that the

respondent feels under pressure (negative end of the scale). When this coding was reversed, the item's Cronbach's alpha increased to 0.38, which did not meet the reliability threshold and indicate that this construct requires further work.

The direct measure of perceived behavioural control did not reach reliability level: Cronbach's Alpha was .20 (.231).

There is a positive correlation between direct (M = 5.73 SD = 0.74) and indirect measures of *attitude* (M = 45.77 SD = 17.24) , $r = .678$, $p = \leq .01$, $n = 27$ - which indicates that both are reliable measures of *attitude* as a construct. Within this correlation, the major contributing factor appears to be the outcome evaluations (as a multiplier of behavioural beliefs), r=.876. $p = \leq .01$.

Similarly, although direct measure and indirect measures of subjective norms do not show a significant correlation (r= -.007, possibly due to the low reliability value of the direct measure), there are several strong correlations both within and between normative beliefs and motivation to comply (as components of indirect measure of subjective norms (Table 16)

The data shows a significant correlation between items 13, 15 and 16 as measures of normative beliefs and items 24, 26 and 27 as measures of motivation to comply. Items 15 and 15 corelated strongly with both items 24 (r=.562, p = ≤ .01) and 26 (r=.561, p = ≤ .01), which suggests that awareness about normative beliefs is stronger than the motivation to comply. This also could have implications in relation to potential correlations between indirect measure of subjective norms and perceived behavioural control. Speculatively, if may mean that normative beliefs about own clinical experience are stronger than motivation to comply with other psychiatrists' prescribing behaviour and the influence of NICE guidelines.

Table 16.

Intra and inter-item correlation for indirect measures of subjective norms

Correlations

		@13	@14	@15	@16	@24	@25	@26	@27
@13	Pearson Correlation	1	-.038	.527**	.567**	.351	.427*	.287	-.057
	Sig. (2-tailed)		.850	.005	.002	.072	.026	.147	.778
	N	27	27	27	27	27	27	27	27
@14	Pearson Correlation	-.038	1	.147	.173	-.125	-.057	.132	.450*
	Sig. (2-tailed)	.850		.463	.387	.535	.776	.513	.018
	N	27	27	27	27	27	27	27	27
@15	Pearson Correlation	.527**	.147	1	.859**	.562**	.070	.561**	.125
	Sig. (2-tailed)	.005	.463		.000	.002	.729	.002	.534
	N	27	27	27	27	27	27	27	27
@16	Pearson Correlation	.567**	.173	.859**	1	.604**	.189	.687**	.210
	Sig. (2-tailed)	.002	.387	.000		.001	.345	.000	.294
	N	27	27	27	27	27	27	27	27
@24	Pearson Correlation	.351	-.125	.562**	.604**	1	.054	.629**	.236
	Sig. (2-tailed)	.072	.535	.002	.001		.790	.000	.236
	N	27	27	27	27	27	27	27	27
@25	Pearson Correlation	.427*	-.057	.070	.189	.054	1	-.207	-.350
	Sig. (2-tailed)	.026	.776	.729	.345	.790		.300	.074
	N	27	27	27	27	27	27	27	27
@26	Pearson Correlation	.287	.132	.561**	.687**	.629**	-.207	1	.541**
	Sig. (2-tailed)	.147	.513	.002	.000	.000	.300		.004
	N	27	27	27	27	27	27	27	27
@27	Pearson Correlation	-.057	.450*	.125	.210	.236	-.350	.541**	1
	Sig. (2-tailed)	.778	.018	.534	.294	.236	.074	.004	
	N	27	27	27	27	27	27	27	27

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

For perceived behavioural control, outcome data is less coherent, but shows no strongly negative correlation. It appears that the control factors identified in the thematic analysis did not capture adequality all the important considerations relating to perceived behavioural control as a construct, and the lack of correlation between direct and indirect measure is attributable both to low Cronbach's alpha reliability of the direct measure (.20) and to the weak intra item correlations of indirect measures.

In the overall exploration of correlation between variables (Appendix H), strong correlations have been observed between the direct measures of attitude and indirect measures of subjective norms (r=.498, p==.008), in particular with the motivation to comply (r=.391, p=.044). This may mean that the perception of the drug of their choice as safe, efficacious and research evidenced correlates with the weight the respondents attribute to actions of other psychiatrists and the need for patient's approval.

Direct measures of attitudes also correlated with generalised intention (r=.589, p=.001), and indirect measures of attitude correlate with generalised intention (r=.381, p= .05) and the intention statement (r=.491, p=.009) – which is a good indicator that the TPB framework is suitable for this investigation and *attitude* is a predictor of *behavioural intention*.

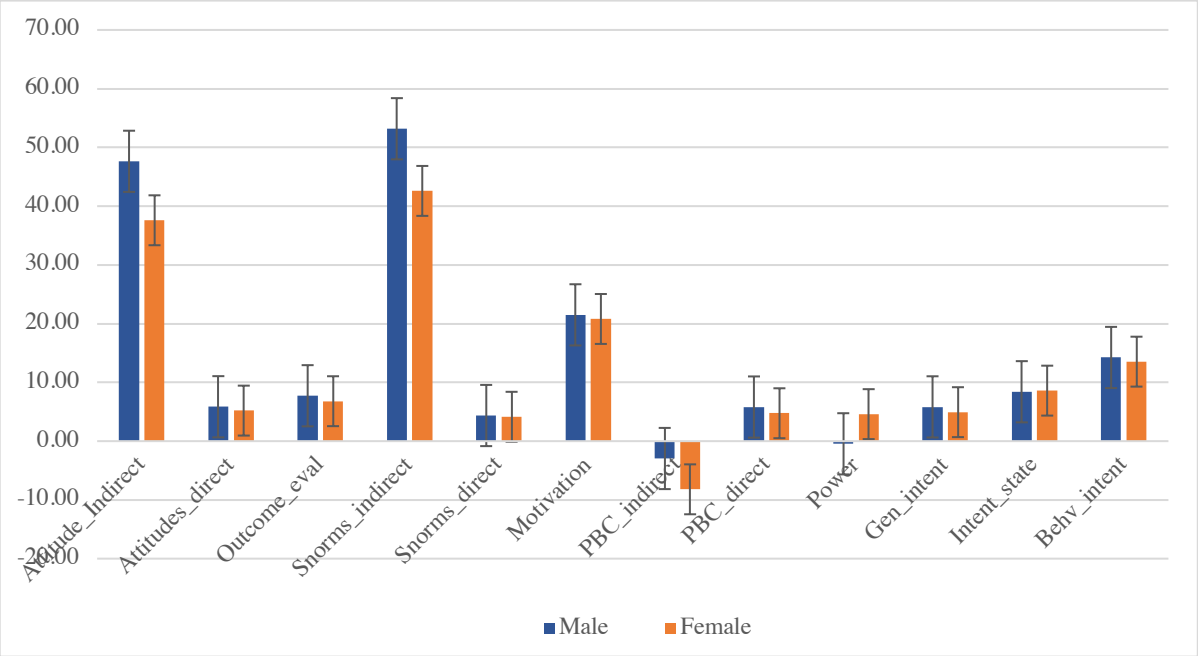
Indirect measures of subjective norms correlate with direct measures of perceived behavioural control (r=.433, p = ≤ .05) and strongly with all measures of behavioural intent generalised intention (r=.555, p =.003) and intention statement (r=.535, p=.004) – with possibly the strongest component being motivation to comply (r=.585, p=.001). Direct measure of subjective norms correlate only with the generalised intention (r=.533, p=.004), possibly due to a lack of correlation between direct and indirect measures of subjective norms construct.

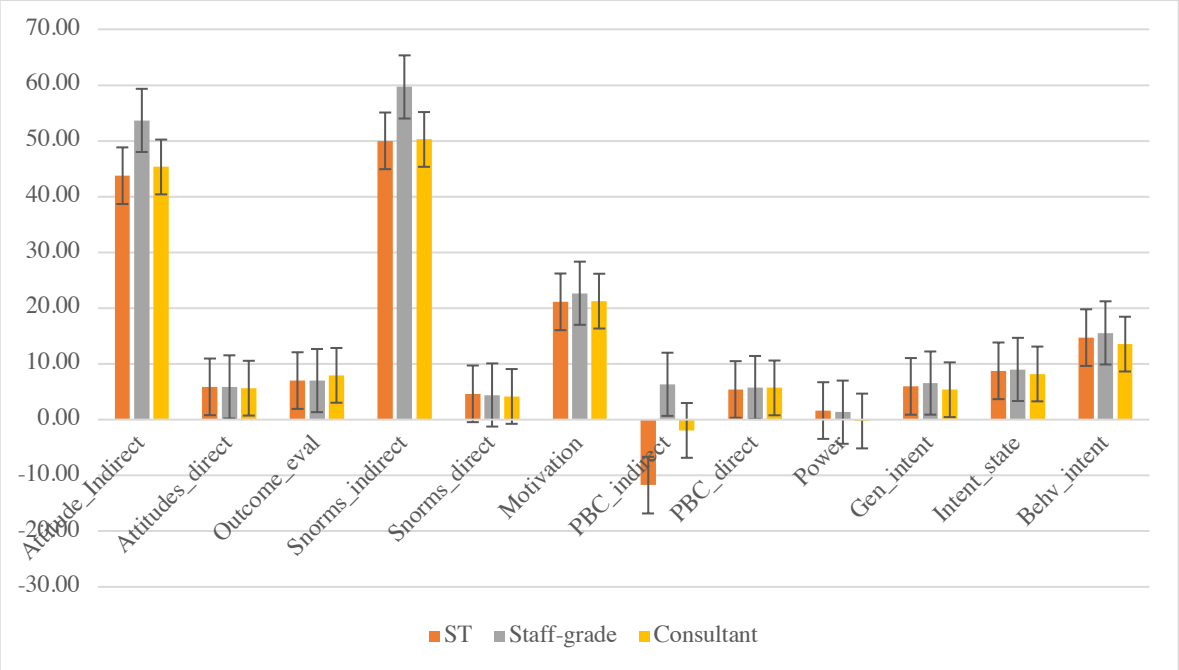
An independent samples test was conducted to establish whether there is a statistically significant difference between the means by gender. A small gender effect was found only for direct measures of perceived behavioural control, with males scoring higher than females; this test has shown some interesting tendencies, but this is inconclusive as Levene's test for

equality of variances is not significant given the small sample size (Figure 18). Similarly, a one-way ANOVA to determine whether there are any statistically significant differences between the means by status (training-grade, mid-grade, consultant) or experience (qualified 1-5 years, 6-10 years, over 10 years) showed no differences between groups in any of the constructs (attitude, subjective norms, perceived behavioural control). There are two possible explanations for this. The first one, and the one which is more plausible is that the sample, size is too small to detect and differences. Conceptually, the second explanation for 'no difference' could be an indication that neither gender nor experience or status have a relationship to the validity of the construct – which is an encouraging result. This assumption however must be treated with caution as methodologically, the absence of evidence is not synonymous to evidence of absence, irrespective of how attractive this may appear in support of the robustness of the questionnaire constructs. The effect differences in perceived behavioural control are not statistically significant but potentially indicative of a trend that would warrant further exploration.

Figure 18

Exploration of the gender and status effect between constructs





Discussion

The aim of the study was to establish whether it is possible to build a questionnaire based on the Theory of Planned Behaviour (Ajzen, 2006) framework using factors identified in the thematic analysis to support the TPB constructs of attitude, subjective norms and perceived behavioural control – and to determine whether this questionnaire would have the internal consistency, validity and reliability required to enable its use in determining the proportion in which attitude, subjective norms and perceived behavioural control will influence behavioural intent in different groups.

Results show that factors identified in the thematic analysis as behavioural beliefs and outcome evaluations (most frequently perceived advantages and disadvantages related to reducing positive symptoms, ascertaining efficacy, considering side-effects, etc.) are reliable and valid measures of *attitudes* – but the study did not demonstrate the same for subjective norms and perceived behavioural control. The fact that the results showed that attitudes correlate with indirect measures of subjective norms, in particular with the motivation to comply signified that there is a relationship between the respondents' attitudes and the opinions of other psychiatrists and patients. Attitudes towards prescribing the drugs were shaped by beliefs that they have a positive effect for the patient, are likely to reduce positive symptoms early on, will keep side-effects at a minimum and efficacy can be established fairly quickly – and by outcome evaluations surrounding the importance of the above factors. These beliefs formed or were reinforced by the clinicians' own experience or under pressure from peers or patients. The approval of colleagues and patients as well as being seen as compliant to guidelines and research evidence is an important contributor to the beliefs held about the safety and efficacy and/or desirable/undesirable effects of prescribing antipsychotics. Attitudes also correlated with behavioural intent which provides a powerful argument to support the use of TPB as a suitable framework to assess the impact of each construct in

different groups. Given the internal consistency of the scale with the TPB framework and its correlation with behavioural intent it can be said that attitudes held about the prescribing behaviour will be a predictor of their intention to prescribe the drugs of their choice.

Subjective norms as an illustration of the respondents' own view on the social pressure on their prescribing behaviour (i.e. the normative beliefs on whether the most important influencers would approve or disapprove of the prescribing behaviour and the motivation to comply with these norms) were a less reliable construct. The direct measures showed no construct validity and require more work, to establish whether the codes/themes identified in the thematic analysis bear no relevance as direct measure of subjective norms or the correlation between direct and indirect measures was incorrectly derived.
The indirect measures showed internal consistency (correlations both within and between normative beliefs and motivation to comply). The results indicate that respondent believe that colleagues, patients and NICE encourage prescribing atypical antipsychotics, but the item with the highest factor validity highlighted that the key source of social pressure came from colleagues. This is an interesting observation seeing that the motivation to comply correlated with attitudes, meaning that behavioural beliefs that shape attitudes will be most strongly influences by colleagues, and not so much by patients or by guidelines and evidence. This finding supports the results of the thematic analysis and serves as a confirmation that the factors were correctly identified.

For perceived behavioural control, the control beliefs (the barriers or facilitators of the prescribing behaviour) identified in the thematic analysis did not satisfy the validity of the construct. One potential explanation is that the way in which psychiatrists conceptualise the notion of control may have been a confounding factors that warrants further exploration: for

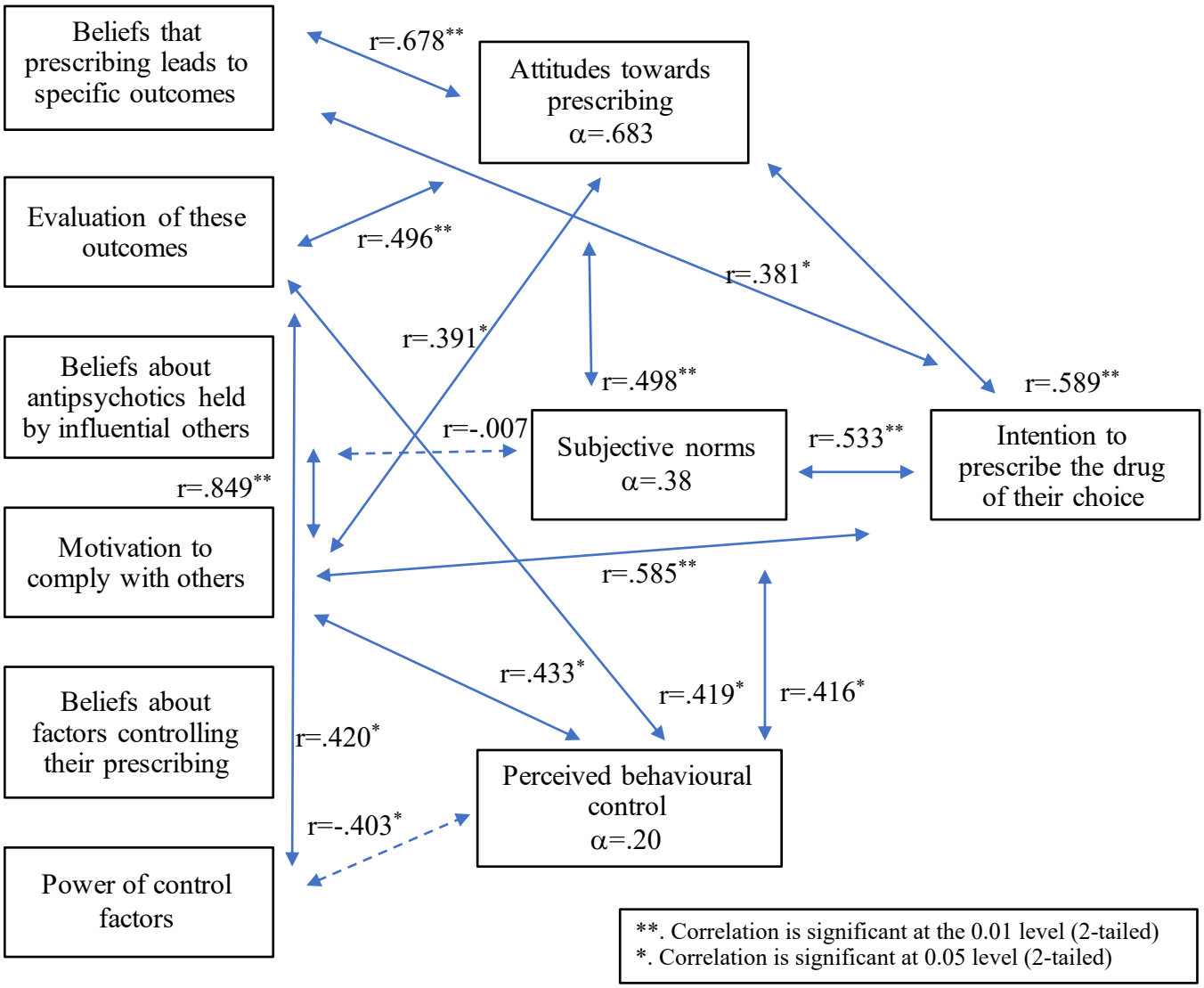
example, they may feel that prescribing a drug from the blue list is within their control but difficult to carry out due to additional administrative burden. However, the power of control factors were the primary influencers of control beliefs and the item with the highest item validity was an acknowledgment that side-effects are a deciding factor in the likelihood to prescribe an atypical antipsychotic, and lack of sufficient information about the patient's presentation was the main barrier to self-efficacy. Their perception of the drug's effectiveness seems to weight less.

The correlation between subjective norms and perceived behavioural control and behavioural intent provides additional support for the utility of the TPB framework - as it indicates that attributing importance to own clinical experience or following the model proposed by peers is likely to be related to either self-efficacy or perceived power of influencers and will direct the behavioural intent. For example, normative beliefs in relation to the importance of doing what colleagues are doing correlates with the confidence the respondents have that they can prescribe the drug if they wanted to. This then translates into a behavioural intent, an expectation to prescribe this drug for each patient with a typical presentation of schizophrenia.

The results of the study can be summarised in a path model (Figure 19) and suggest reoccurring themes that beliefs are reinforced by the motivation to comply with sources of social pressure and a good indicator of prescribing behaviour. The power attributed to control factors is inversely proportional to perceived behavioural control and are not a determinant of behaviour.

Figure 19.

Reliability of measures and construct correlation



These findings replicate only partially the findings of previous studies, and more work is required to ensure construct validity for subjective norms and perceived behavioural controls as well as correlations between direct and indirect measures within the construct. [14]

[14] Apart from Ajzen's own work describing the construct and evaluation of the questionnaire and the Francis et al. manual there are very few studies describing the and evaluating the design and acceptably of a TPB questionnaire, most of the published literature reflects the use of a TPB questionnaire to predict behaviour and offers little information on how the questionnaire wa

A study by Russo et al., (2012) using the Theory of Planned Behaviour to assess factors influencing the identification of individuals at ultra-high risk for psychosis in primary care used the same steps in designing and evaluating the reliability of a TPB questionnaire and showed reliability for all direct measures (α0.77–0.87). The path analysis models showed that all the TPB constructs were significant predictors of intention. The study used self-reports as measures of beliefs and intentions to construct direct measures and this is different from the TYPCASt study which uses items identified in thematic analysis. It can be inferred therefore that a more systematic approach is required to identify positive and negative items that contribute to each construct.

Limitations

The main limitation in conducting this study is that its scope was reduced to 'proof of concept'. The aim was to test whether a reliable questionnaire can be constructed using the TBP framework to test the hypothesis that factors which shape prescribing behaviour are present in different proportions or are given different weight for each 'typology' of prescriber. Constructing the questionnaire is an methodologically integral part of this work and factors identified in the thematic analysis provided the material which otherwise TPB stipulates that should be obtained in an elicitation study. These were then used to build the direct and indirect measures of attitudes, subjective norms and perceived behavioural control. Whilst the Theory of Planned Behaviour confers a robust external validity to instruments constructed in this framework, the internal validity of the constructs can be a confounding factor. In the results presented from this pilot study, the lack of correlation between the direct and indirect measures for subjective norms and perceived behavioural control reduced it's testing scope, as in essence it could not be demonstrated that the factors derived from the thematic analysis can be used to construct a valid questionnaire.

This lack of correlation may be due to the fact that not all the important considerations relating to influencers or control factors were identified during the elicitation phase. As the study used the thematic analysis in the TAnDeMS study to extract the relevant factors this may have been a constraint resulting from either study design or conduct. Some relevant items may have been removed during the refinement phase in the attempt to produce a questionnaire of acceptable length. Another possible explanation is that clinicians' perceived control beliefs in relation to antipsychotic prescribing may be ambivalent if they believe (which they do) that antipsychotics are likely to have positive as well as negative outcomes – and the data showed this correlation between perceived behavioural control and outcome evaluations. Last, the way in which *control* is conceptualised by psychiatrists may have been a confounding factor: listing the items that aimed to ascertain that the prescribing behaviour is under their control (the ability to prescribe if they wanted to) after the items that measured the power of control factors (I am less likely to prescribe these drugs if I feel rushed into a decision) may have skewed the answer by prompting the respondent to think more about the power of control factors. Boyko, Lavis, Dobbins, & Souza (2011) suggest that it is necessary to explore the internal consistency and test-retest reliability of TPB constructs and advocate that that reliability of the constructs (attitudes, subjective norm, perceived behavioural control) would be strengthened if they were measured on more than one occasion.

Sample size is also an important consideration: Flowers, Freeman, & Gladwell, (2017) suggest that a minimum of 25 participants are necessary to ascertain salient beliefs via the elicitation study and a further sample of 250 participants is necessary for each of the refinement stages and the validation stages. As the current study has had 11 participants in the elicitation study, a further 11 participants in the refinement stage and a further 27 participants in the validation stage, it falls short of the required sample size. Despite persistent efforts and a variety of strategies employed the response rate has been rather poor,

and the low response rate had to be acknowledged as one of the major limitations of the study. However, as this is only one phase in the development of the questionnaire, an exploratory developmental phase, not the application of the instrument itself in a confirmatory study, there is still scope for analysing the data to understand how correlations develop. The concern about the low response rate is thus not necessarily related to the sample size, but more importantly to the fact that we don't know how the respondents may differ from the non-respondents. It is not possible to ascertain the characteristics of the non-respondents' group, but it can be inferred that if they had a different set of behavioural, normative and control beliefs this may have had an impact on the internal validity of the questionnaire. There was however a sufficient breadth of respondents' experience and status to confer some degree of stability to the construct and enable the exploration.

Despite the limitations, the major strength of the study rests with the psychometric evaluation properties of the constructs. It provides the basis of an empirically-supported method to test quantitively factors identified in a qualitative study. TBP questionnaires are widely used in evaluating a variety of behavioural intents but the majority of TPB questionnaires are used only once, in specific populations to determine specific behaviours and a psychometric evaluation of the instrument is not carried out (French, Cooke, Mclean, Williams, & Sutton, 2007). The results of the study demonstrate unequivocally that it is possible to use the factors identified in the thematic analysis as attitudes towards antipsychotic prescribing, behavioural beliefs and outcome evolutions of this behaviour (prescribing the drugs of my choice is safe, efficacious, evidence-based and likely to do something positive for the patient – or not) as a direct predictor of behavioural intent. Another important aspect identified in the study is that subjective norms, and in particular *motivation to comply* correlate with *attitude*; due to the small sample size it was not possible to attempt to demonstrate with statistical significance that this has a causative effect, but it is

possible to see a link between attitude and motivation to comply contributing to the behavioural intent – and this demonstrates that it is possible to use the TPB framework to look at how various factors influence each other in decision-making. More work is require to achieve full internal consistency of the questionnaire, starting with validity of direct measures for subjective norms and perceived behavioural control, as well as a more robust correlation between direct and indirect measures of these constructs, but essentially we now know that it is possible.

The other encouraging prospect is that the questionnaire demonstrated a very small gender effect and no effect of experience or status on the other variables. This aspect requires further investigation to ensure a robust testing, but for now it compares well with the findings of the qualitative study, that experience[15] and place taken in the hierarchy do not influence prescribing behaviour in the same way as attitudes to risk, knowledge and utilisation of research evidence, perception of efficacy/side-effects. Both senior and very junior clinicians can have the same factors influencing their prescribing behaviour in the same way.

The next step would be to complete the validity and reliability work. Once a revised questionnaire has been validated, it could be used to compare variables between groups. The factors identified in the thematic analysis which ascribed behaviour to patterns labelled the 'high-flyer', 'skeptical experimenter', 'rule bound' and 'systematic conservative' can be added to the demographic section of the questionnaire to allow data analysis comparatively by group. For example, the demographic section could ask questions relating to attitude to risk, perception of efficacy vs side-effects, knowledge of research evidence and views relating to patient involvement.

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[15] 'experience' in this context does not equate to 'clinical experience' it is merely used to denote the number of years of presence in the field, i.e. years since qualifying – for lack of a better word. This may need to be reworded in a future study to avoid any confusion with 'clinical experience' denoting the sum of skills and expertise acquired in treating a particular condition.

Path analysis could be used to test a variety of hypotheses, such as

H_0: there is no difference between groups and attitudes, subjective norms and perceived behavioural control are all predictors of behavioural intent

H_1: in the 'high-flyers' group, attitudes are the strongest predictor of behavioural intent; subjective norms and perceived behavioural control do not significantly correlate with behavioural intent.

H*2*: in the 'systematic conservative' group, subjective norms are the strongest predictor of behavioural intent, etc.

Francis et al., (2004) advise that to determine which specific beliefs have the greatest influence on intention, the intention variable has to be either classified on a zero/>0 basis (non-intenders, intenders) or dichotomised using a median split (low vs high intenders) and then using t-tests or discriminant analyses to identify those beliefs that discriminate between the groups.

Ajzen (2006) highlights that each construct (attitude towards the behavior, subjective norm perception of behavioral control and intention) reveals a different aspect of the behavior, and *"each can serve as a point of attack in attempts to change it".* If we know the underlying foundation of behaviors, we can determine the how to act to change the course of action. This does not mean that we need to change how psychiatrists prescribe but we can use this information about the determinants of behavior to improve knowledge transfer, uptake of research evidence or support a better model of patient interaction to improve the patient's journey.

CHAPTER V.

Critical review, potential impact of the findings and scope for future work

> *"It doesn't matter how beautiful your theory is, it doesn't matter how smart you are. If it doesn't agree with experiment, it's wrong. In that simple statement is the key to science"*
>
> *Richard Feynman, Cornell University Lecture, 1964*

This thesis aims to bring together several strands of investigation to explore the factors that contribute to decision-making in prescribing for schizophrenia and hypothesize how understanding these factors could be used to improve knowledge translation models.

The first study aimed to provide empirical confirmation to the anecdotal evidence that atypical antipsychotic prescribing is on the rise. The literature published up to 2012 and an exploration of Prescription Cost Analysis data for antipsychotics between 2006 and 2014 demonstrated an increase in atypical antipsychotic prescribing from 21% (of total antipsychotic prescribing) at the end of January 2000 to 79.9% at the end of December 2014. The initial momentum may have been the result of the research evidence and first NICE guideline, but if the principles of evidence-based practice were followed, the prescribing trends should have shown a decrease of atypical antipsychotic prescribing and a reciprocal increase in typicals; this decrease should have continued as research-evidence on safety and efficacy of antipsychotics accumulated, which placed some typicals on a superiority efficacy position. The PACE study showed that this was not the case and concluded that de-facto prescribing does not follow research-evidence solely.

The TAnDeMS study started from the premise that if new research evidence on its own is not sufficient to change practice there must be some other factors involved, which obstructed

knowledge translation and implementation. Thus, the study aimed to identify factors that contribute to decision-making and whether these factors influence each other in a specific way. The study found that when research evidence has a degree of methodological uncertainty or is subject to radical change, the decision is made by experience rather than by utilising new evidence. Factors that influence how decision is made pertain to perception of risk, degree of use and interpretation of research evidence, requirement for further information on patient's presentation and circumstances, personal experience and preferences/ routines in prescribing, views on importance of efficacy vs probability of undesirable side-effects – but more importantly the study identified that these factors interact in a specific way and coalesce around potential behavioural models. Ownership of the decision-making process stems from attitudes and beliefs - and to some extent from clinical experience; clinical experience not research evidence dictates treatment plan and the onus for 'translating' evidence findings is placed on others. The value attributed to information is proportional to the perceived authority and power of the 'source'; some parts of the decision-making process depend on collaboration with peers, most often part of a risk management strategy. The way in which these factors interact does not follow a linear model, but it is 'messy' and there is a lot of 'noise' in the system, in particular around the validity of research evidence; people will meld information, interpret and 'translate' it and corrupt it in the process, especially when the appears to contradict their own clinical experience.

In parallel, the TAnDeMS study has also shown that the practice of EBM has limited integration with person centred care, and whilst the patient is central to the decision-making process, patient involvement can be somewhat tokenistic and serves other purposes, such as mitigating risk, gaining therapeutic alliance or medication compliance. Integrating person-centred outcomes in 'research evidence' is imperative.

The follow-on TYPECASt study aimed to test these potential behavioural models, to identify whether they have generalisability value, in a Theory of Planned Behaviour framework. A questionnaire was constructed using a manualised method and used the data from the thematic analysis to define attitude, subjective norm and perceived behavioural control items. The validity and reliability of the instrument was tested and results showed that the model itself is a suitable tool to test the behavioural models hypothesis, but only attitude items had reliability value. As this was an exploratory, proof-of-concept study and the sample size was limited, no generalisability statements can be made based on these results. However, even in a small sample size trends have been identified that confirmed that it is an avenue worth pursuing. There are strong correlations between attitudes and behavioural intent, and motivation to comply has also been shown to have a directly proportional effect. The implications of these partial findings are that if a fully validated instrument would be able to identify which of the factors influence behavioural intent in different groups.

Ilyas & Moncrieff (2012) attribute the rise in antipsychotic prescribing partly to longer-term treatment and increasing population, some off-label use of low-dose formulations, but more importantly, to prescribing levels of antipsychotics exceeding recommended limits. [16] Taylor, Mir, Mace, & Whiskey (2002) have identified that *'irrational prescribing'* could be the result of the anxiety and stress of bearing responsibility for this group of patients and Moncrieff (2009) argues that if this is the case then psychiatry is guilty of *"gross scientific misconduct",* and examining long-term effects of antipsychotics Moncrieff states that *"It is as if the psychiatric community cannot bear to acknowledge its own published findings",* casting doubt of the use of EBM in psychiatry. This view adds momentum to re-examining the EBM

[16] This view is supported by Healthcare Commission report (2017) which indicated that as high as 40% of patients treated for psychosis have been prescribed higher than recommended limit doses, likely to cause severe side-effects.

concept, and if clinical decision-making *is* informed by evidence, then what constitutes evidence and how is it utilised depends on very specific individual factors. These factors form distinct 'patterns' - and if these patterns withstand the test, this would allow targeted interventions to facilitate knowledge translation and implementation in a different way than our established strategy of cascading clinical guidelines. Grimshaw, Eccles, Lavis, Hill, & Squires (2012) suggest that 'knowledge translators' need to acknowledge that key messages will vary by the type of research and different endpoints may apply to different target audiences and therefore key messages need to be tailored to meet the need of the audience. This is not a new view, there are a large number of knowledge translation models which stipulate that barriers and facilitators have to be identified and the choice of strategy is informed by these assessments, but there is a paucity of literature on the effectiveness of different strategies to overcome specific barriers.

Michie (2004) maintains that behavioural interventions should be key to implementation and cascading guidelines in a way that increases behavioural specificity could be a very effective method of increasing knowledge translation and implementation. If behaviours could be precisely specified, it is more likely that they will be carried out, and to this end behavioural analysis of the *"controlling antecedents and consequences of implementation"* will help develop effective interventions.

For the reasons above the factors identified in the thematic analysis will map out the behavioural, normative and power beliefs (controlling antecedents) and outcome evaluations as (consequences of implementation) – and in addition (if the factors withstand the quantitative testing) will map the key messages and different endpoints for different audience segmentation groups.

This is equally true for de-implementation and this must be considered when so much of the antipsychotic prescribing seems to be attributable to vestiges of superseded evidence. If this

is a limitation of EBM as a concept is uncertain, but Greenhalgh et al. (2014) identify several points that narrowed its usefulness and relevance, amongst which the volume of evidence that needs to be considered as *"unmanageable and unfathomable"* and a poor fit for real-life patients with multimorbidity who often do not fit text-book definition of the condition and certainly differ from those in clinical trials. To redress the balance, EBM should individualise evidence, put a greater emphasis to patient factors in a true patient-centred approach and ensure that clinical experience is characterised by expert judgment rather than mechanistic algorithm following.

Another possible route of further exploration is to question whether in the context of so much methodological doubt in research evidence and such fluidity in recommendations we do need at all the implement guidelines at all costs.

As in Hume's guillotine, where it *"seems altogether inconceivable how this new relation can be a deduction from other which are entirely different from it",* if guidelines are made from lots of excellent observations on how things are, does not necessarily follow that all patients should be treated in accordance to this evidence.

The questions will always be there that the guidelines might be wrong or that by the time it took to implement the guideline by navigating all the steps of the implementation framework the 'knowledge' on which they are based will be outdated. Because knowledge translation takes too long and it depends on so many factors and because evidence is never static, by the time we implemented it the evidence supporting it will have changed. Thus, if practicing EBM is truly the goal, we need a system to do it fast and be prepared that it may change; systems inertia required to set things up may need to give way to a more malleable system, amenable to swift change and this has to account for the attitudes and beliefs, subjective norms and other the factors identified and discussed in this study. The question remains then

if it is time to reduce the complexity of implementation strategies to a novel model of 'spreading good practice' by understanding behavioural patterns and using appropriate influencers to either cascade evidence into practice or de-implement superseded evidence.

The debate on de-implementing superseded evidence is particularly relevant in the context of recent advances in the role of dopamine signalling and the utility of antipsychotics in schizophrenia. Despite confirmatory evidence for the dopamine hypothesis, it is still not properly understood why, how and when dopamine alterations occur in the brain, or their relationship with the diversity of symptoms in the disease, which make almost every patient a distinct presentation. De-implementation of current treatment models will be required as novel therapeutic approaches look at targeting dopamine signalling to improve the limitations of current antipsychotic drugs and personalised treatment approaches are being developed based on genetic variants characterising the clinical features.

In the move towards a person-centred approach, it would appear the EBM looses conceptual validity, especially in psychiatry. Several assumptions of evidence-based approach, such homogeneity of condition and 'more data' equated to 'better' evidence, turn out to be reductionist. Patients are all different and the condition as experienced by the patient is a sum of bio-psycho-social factors that interact differently for each individual. The Person-centred approach acknowledges a multi-factorial model and complexity of causation and presentation.

At the same time, delivering person-centred care is as much about the clinicians as it is about the patient. If EBM imposes a lack of autonomy for the practitioner and implies that the dogma of 'best available' evidence *should* be followed, it will invariably downgrade clinical experience as there is less room for practical judgement when medicine is expected to deliver

de-personalised and standardised treatment, with science and humanism viewed as distinct domains and a dichotomy between cure and care.

Although viewed as ontologically distinct, Evidence Based Medicine and Person-Centred Care can be integrated, if middle ground can be found in what we define and accept as evidence, in giving more power to clinical experience to integrate this evidence with patient specific factors which are derived from a true understanding of the significance of heterogeneity from the patient's perspective. I am not advocating that clinicians should ignore research evidence, but it is time to acknowledge that 'horses for courses' approach is preferable to the tyranny of hierarchy of evidence, and recommendations based solely in the strength of evidence being derived from large numbers of observations /intervention outcomes. At the same time guidelines produced for single conditions / disease might need to change to consider co/multi-morbidity, and acknowledge that the biomedical model will not work infallibly when patients' presentations are so diverse.

I would argue that evidence-based medicine and person-centred care are in fact not dichotomous. To explore this we need a better understanding of the fact that 'knowledge' can not be totally grounded in 'evidence synthesis' (and the study has showed that participants doubt the value of empirical research or re-interpret it in a confirmatory bias) and actions are directed by a subjective perception/ personal view of harm vs benefit. The weight attributed to patients' views also differ – naturalistic fallacy supports the idea that no 'fact' is 'value' free and even most "scientific" of disciplines are affected by the "values" of those who practice it. If both the patient and the clinician have access to best available evidence, and there is mutual consideration for the patient's lived experience and the clinicians knowledge and expertise, care is co-produced rather than provided by the clinician and accepted by the patient.

In this context, if a new paradigm were to combine the two approaches the information brought by this study should go some way towards understanding how individual attitudes and values influence behaviour.

Reflective diary: a personal journey

This had been a long and challenging rite of passage, yet strangely satisfying. My previous doctoral journey some 20 years ago was fraught with entirely different challenges and naively I believed that a 'more mature me' was ready for a new journey of discovery. The topic was fascinating and I wanted this thesis to be my 'apprentice piece' and my entry exam to the Guild of Scholars. I paid no attention to my friends' warnings that such an undertaking is a bit like deciding to have a baby: wonderful at the point of conception but the delivery is an entirely different matter – and so it was. The enthusiasm with which I launched in this enterprise would have been chipped away by the inherent difficulties of conducting research, if it was not for the endless learning opportunities this project gave me. I learnt about the intricacies of qualitative research methodology and the opportunities it brings to the map of research evidence. Listening to what my 'research participants' had to say and then using the newly acquired skill to turn discourse into themes and meaningfully extract items that can be built upon and speculatively conceptualised, was one of the greatest joys. I also found that 'real-world research' requires a fundamental reconsideration of style and approach when dealing with such complex, messy and 'poorly-controlled' field setting and there is no one 'cook-book' with neatly laid out instructions to follow.

I discovered with humility that my knowledge about what it takes to synthesize evidence into guideline was somewhat limited and did my very best to polish up – and used this upgraded skill to contribute (quite separately from this project) to evidence synthesis for the National

Collaborating Centre for Cancer that fed into two NICE guidelines. This has helped me to better understand how to deal with the lack of evidence to support the evaluation of implementation uptake for the NICE schizophrenia guideline, and the real lack of coherent year-on-year data in relation to antipsychotic prescribing.

Whilst collecting data and writing up I discovered that information had a perishable quality that I had not acknowledged before. By the time I got to write up my analysis of prescribing trends the data was already 4 years old (2006 to 2010) and did not make a very clear point, so I had to add to it a new set of data (2010 o 2014) which I did not initially anticipate. The same happened to my literature review for comparative studies of safety and efficacy of typical vs atypical antipsychotics. I had written up the chapter at the beginning of the study, but when time came to integrate the findings into the rest of the project the studies that I so painstakingly reviewed were out of date and superseded by more recent evidence. Far from being a bad thing, this has given me a 'first-hand' insight into how the guideline developers must have felt about their painstakingly reviewed evidence that was out of date or (with the benefit of hindsight) methodologically challengeable.

Methodological aspects aside, I learned that the practicalities of conducting research never change and convincing data custodians to allow access to their data is not getting easier, and neither is recruiting participants.

Most importantly, I learned about the place of unconventional thinking in scientific enquiry and how to allow critical thinking to constructively shed light on some controversial issues. In the same context, one of the more valuable lessons was to learn how to exercise restraint: as I was progressing thought the enquiry so many different avenues of exploration opened that made for a tough decision in choosing what to delve into and what to set aside for another day. I would have wanted to look closer to how attitudes about antipsychotics are

formed in the first place and to understand what makes some psychopharmacologists such devoted supporters of a particular class of drugs – and it would have been very useful to have the time (and space within the scope of the PhD) to explore the poor uptake of psychological interventions in psychosis and the reluctance in advocating it despite the support of the NICE guidance.

On a personal level, I discovered I had a great gift for procrastination and managed to give meaning to most mundane activities to save myself from writer's block or gather momentum to tackle some of the more difficult points of this project.

It also gave me great pleasure to find out that my enthusiasm was contagious to younger students with whom I shared the topic (and my data). For this alone I would do it all over again.

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APPENDIX A.

Participant Information Sheet – TAnDeMS study

COLEG IECHYD A GWYDDORAU YMDDYGIAD
COLLEGE OF HEALTH & BEHAVIOURAL SCIENCES

YSGOL GWYDDORAU MEDDYGOL
SCHOOL OF MEDICAL SCIENCES

PRIFYSGOL
BANGOR
UNIVERSITY

Prescribing in Schizophrenia: A Think-aloud Study

Participant Information Sheet

We would like to invite you to take part in our research study.
Please read this information sheet carefully before deciding whether or not to participate and please do not hesitate to contact us, should you require further information or clarifications.

What is the aim of the study?
This is a hypothesis-generating study into the "decision-making" process and knowledge translation in first-line prescribing in schizophrenia.
This study aims to map the clinical decision-making process and to identify how clinicians use various factors (such as research evidence, things they know about the condition, the patient and the drug which they choose to prescribe) to reach a decision on what to prescribe first-line for a patient presenting with a first episode schizophrenia. The primary aim of this study is to learn more about how these factors interact to contribute to the decision making process.
The resulting data will inform the larger PhD research by Rossela Roberts. The overall aim of the PhD thesis is to look at which factors of the Evidence Based Medicine framework (such as research evidence, patient factors, organisational factors) have most influence on clinical practice in this area.

Why have I been asked to participate?
We are asking all Consultant Psychiatrists and mid-grade doctors in the Mental Health CPG with experience in prescribing for schizophrenia to take part. By agreeing to participate, you will offer an invaluable contribution to this study. Your participation is voluntary and a decision to not take part in the study or to withdraw at a later date will not affect your employment.

What will I have to do if I take part?
If you agree to take part, you will be asked to meet Rossela for the think-aloud study and a follow-up semi-structured interview.
The think-aloud study and interview will take approximately ½ hour to 40 minutes and it can be arranged at a time /place of your convenience. During this meeting you will be asked to look at a vignette describing a patient with a typical fist episode psychosis and you will be asked to 'think-aloud' (i.e. verbalise the though process) the clinical assessment and decision-

making process that you would carry out to ascertain the optimal treatment /care pathway (including what drug to prescribe) for this patient.

Rossela will ask for your permission to record the interview so it can later be transcribed to analyse the text. The analysis will aim to identify several factors which all clinicians have mentioned during the decision-making process.

At the same time you will be asked to participate in a semi-structured interview; the factors you and other clinicians have identified in the think-aloud study will be discussed to you and you will be asked to identify those that you consider to have been more important in your decision-making process; this phase is not anticipated to take more than 30 minutes of your time.

What use will be made of the collected data?
We are aware that we will be exploring a sensitive area, but the intent is to describe the decision-making process, not to not to scrutinise individual prescribing practice, nor to compare prescribing practice between clinicians or between BCUHB sites. The data collected will inform on aspects of evidence considered significant by clinicians; there will be no distinct report written as a result of this study, but the evidence factors identified as significant in the decision-making process will be presented as a poster at conferences and will later be integrated into the PhD thesis. No individual clinician will be identifiable in publications.

Can I change my mind and withdraw from the study?
We hope that you will agree to take part in both the think-aloud study and the interview but you will be able to withdraw from the study at any time, without giving an explanation; if you withdraw from the study the data we collected thus far will be kept and used for the project.

Is my taking part confidential?
Absolutely; with your permission, we will audio record the think-aloud study and the interviews. The audio recordings will be anonymised (identified by a participant study number and not by name) and will later be transcribed for analysis. All data will be stored securely and will be confidential to the academic supervisors (Dr Christoher Burton and Professor David Healy) and to the PhD student, Rossela Roberts, who will collect the data. Only members of the research team will have access to the raw data. In accordance with Bangor University guidance, the data will be kept for a minimum of 5 years, or at least 2 years after the PhD dissertation has been submitted. It will then be destroyed.
If you agree, verbatim quotations from the interviews may be used in publications, but such quotations will be anonymised and will not be identifying the author.
Similarly, the ranking of factors you will make during the follow-up interview will not be attributable to you personally (the response sheets are anonymised and list only a participant number)

Who has reviewed this study?
This project has been reviewed and approved by the Bangor University Healthcare and Medical Sciences Academic Ethics Committee and by BCUHB R&D Internal Review Panel.

What if there is a problem?
If you have any study specific concerns or complaints, please contact the Academic Supervisor, details below. If you wish to raise a concern or complaint with someone independent of the project, please contact the Head of School of Medical Sciences, Bangor University.

Academic Supervisors:
Prof David Healy
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Whom do I contact if I have any questions?
If you have any questions about our project, either now or in the future, please feel free to contact the Academic Supervisors or the Student.

Rossela Roberts
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APPENDIX B.

Consent Form – TAnDeMS study

COLEG IECHYD A GWYDDORAU YMDDYGIAD
COLLEGE OF HEALTH & BEHAVIOURAL SCIENCES/

YSGOL GWYDDORAU MEDDYGOL
SCHOOL OF MEDICAL SCIENCES

Prescribing in Schizophrenia: A Think-aloud Study

Consent Form

Please **initial** the box

1. I confirm that I have read and understood the Information Sheet (Version 2, dated -01 July 2013) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and that my legal and employment rights will not be affected. ☐
3. I agree to the study interviews being audio-recorded in an anonymised format and later transcribed for analysis. ☐
4. I agree to anonymised quotations from the interviews to be published. ☐
5. I agree to take part in the above study. ☐

Name of participant (PRINT)	Signature	Date
Name of researcher (PRINT)	Signature	Date

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APPENDIX C.

Vignettes – TAnDeMS study

"A 21 year old female is admitted to the Mental Health unit out of hours. She has returned to North Wales from her course in Cardiff with a history of deterioration over several months. She has ideas that her computer is being monitored. She is dressed bizarrely, wearing several layers of clothing. Underneath you suspect she is underweight.
She is admitted at a time when the Unit is very full and the ward is disturbingly noisy. Because of a risk of suicide, and concerns she might abscond, she is detained on a Section 3."

"A 23 year old male is referred by his GP, for help with 'paranoia'. He describes how he has become preoccupied with a girl in the factory he works. She knows he fancies her, and has been 'setting him up', to frame him for a criminal act/ public shaming. Looks and gestures passing from her to other workers have revealed their intentions. (He has been raped in the army, and has a morbid fear of being thought homosexual)."

APPENDIX D.

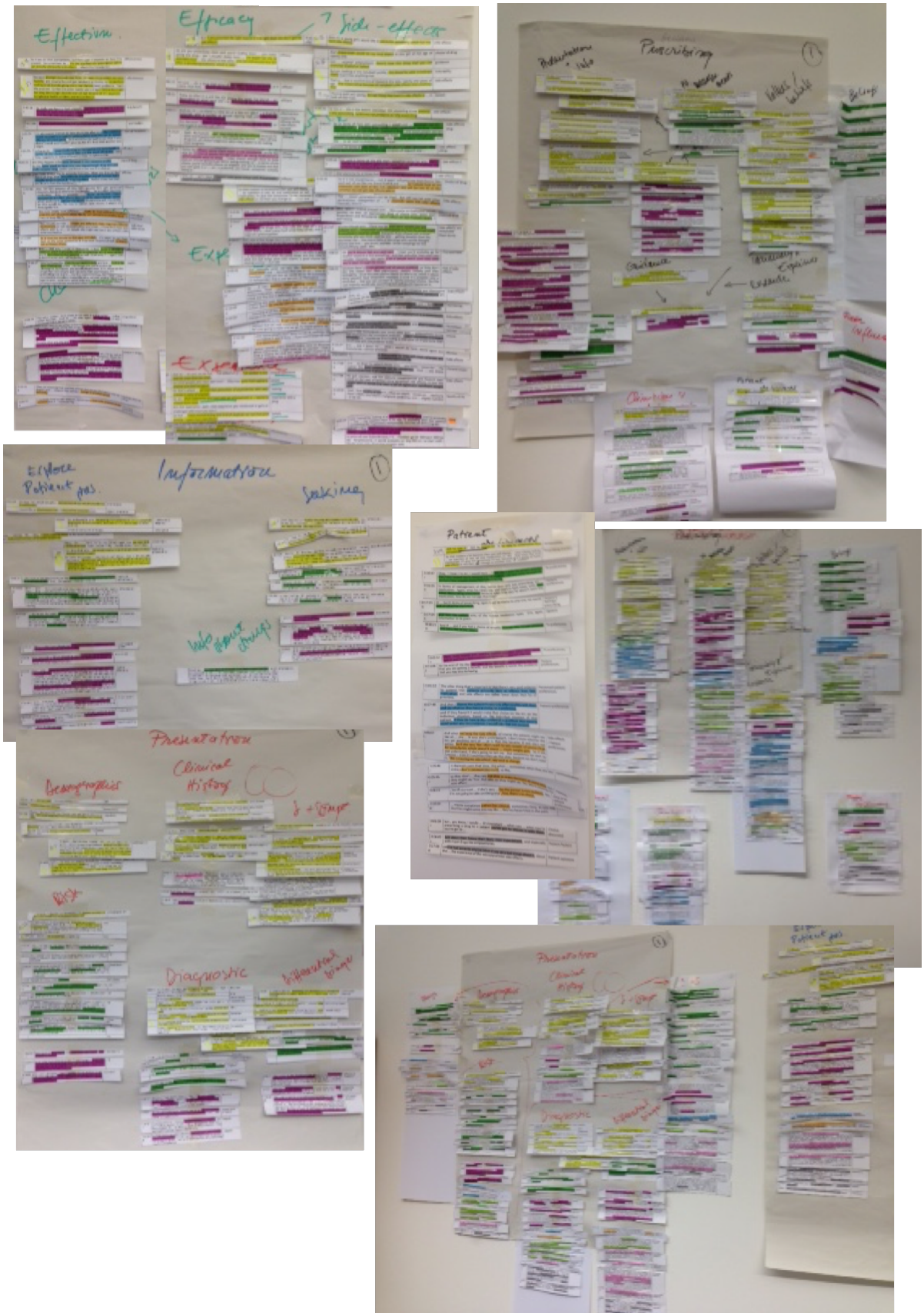
Thematic map – TAnDeMS study

Broad Category	Codes	Description
Evidence	Evidence	Acknowledges research evidence, studies, reviews, meta-analyses mentioned or referred to; assesses value and quantity of evidence available; uses evidence in their practice; importance of evidence, evidence above patient preferences; evidence is flawed, does not trust evidence.
	Clinical guidelines	NICE, Maudsley, RCPsych, etc guidance mentioned; acknowledges current/changes in guidelines; uses guidelines in practice
	Legislation	mentions Mental Health Act or other relevant legislation
	Pharma and regulators	references to pharmaceutical industry /clinical trials
	Drug regulators, MHRA	Clinical trials; regulatory requirements
Diagnostic	Diagnosis	Diagnostic named; differential diagnosis considered/eliminated; diagnostic criteria; uncertainty factors considered; seeking facts to support; seeking test to support; hesitant /cautious approach (‘unknown entity’) or confident about diagnosis
	Information	Have enough information; needs more information; seeks clarification of symptoms; explore Pt. presentation /clinical picture; Information from family, GP and other sources; further information requested from or about the patient; further information necessary/required to reach opinion; challenging existing information
Patient factors	Patient history	Familiarity with patient / patient known, contact with GP, previous treatment; previous experience with a drug
	Patient presentation	Signs and symptoms, complaints, psychological issues, patient’s feelings, experiences, delusions; somatic/metabolic factors; cognitive factors; responses given to clinical queries; trauma; patient misinterpreting things; functional ability; needs sedation; assumptions
	Patient demographics	Demographic details, references to age, gender
	Patient preferences/values	Acceptability/tolerability: will patient take the drug; accept the drug, understand clinician’s perspective; risk discussed with patient; onus on patient to make a decision; beliefs about patient preferences; patient’s concerns about side-effects; patient choices
	Individual response	Response to dose, clinical outcome

Drugs	Effectiveness	Effectiveness of treatment; balance of risks/benefits; measuring effectiveness by side-effects
	Side-effects	List of side–effects; discussion of impact of side effects; safe choice; patient's concerns about side-effects; choice of drug – are side effects a factor?; side effects information is important; uses side effects as proxi measure for treatment adherence strategy
	Efficacy	Clinical outcome great/not so great;
	Dose	High dose/low dose; titration (start low/go slow)
	Acceptability/tolerability	Tolerability; acceptance, compliance
	Drug Information	Describes the drug. facts about its history or method of action
Treatment Plan	Desired outcome	Functional ability; clinical efficacy; avoiding side-effects
	Risk	Risks considered; risk to patient (risk of prescribing/ risk of not receiving treatment); suicide/ absconding; risk to self or others; risk of recurrence; assessing whether it is worthwhile to take the risk; safe choice of drug/ risk from medication/concerns about side-effects; discussing risk with patient / assessing importance
	Clinical Reasoning	Formulating arguments to support diagnosis or treatment plan' differential diagnosis considered
	Clinical Experience	Clinical experience; patterns of behaviour; experience in prescribing a drug; training; uses experience to inform diagnosis or treatment; confidence or a lack of confidence
	Professional attitude	Things considered/explored before prescribing (would like to know); exploring patient's presentation; decision factors; won't prescribe straightaway # drug chosen promptly; professional evaluation/opinion: how is the presentation regarded; paternalism: retains decision control, refuses /debates patient choice
	Own beliefs	Opinions not based on specific information; opinions about other people's beliefs; concerns; strong views beliefs/values/feelings
	Peer influences	What other clinician would do, what does a colleague/senior think; education and training received
	Patient factors	History, presentation, demographics;
	Patient perspective	Patient preferences, desired outcome, priorities; enquires about preferences/feelings about a choice; consider cultural factors; responsive to patient needs.
	Patient involvement	Considers patient's ideas, concerns and expectations; includes the patient in decision-making; the influence of the patient on the participant's practice; importance of patient preferences
	Management	Short term, medium term and long-term solutions; short term sedation; long term outcomes; long term effects; safe environment
	Strategy	How it is proposed to manage patient; treatment plan; how plan is made
	Therapeutic alliance	Discusses strategy with the patient; acknowledges patient preferences, understands patient perspective; informs the patient (explain); gives patient a choice/ options
Education/ Training	Impact	Awareness of the source of their own knowledge and practices; changes in practice following training and teaching

APPENDIX E.

Cut and sort technique used in data analysis in TAnDeMS study



APPENDIX F.

Participant Information Sheet TYPECASt study

Participant Information Sheet

Decision-making process in prescribing for schizophrenia

What is the purpose of this study?

This study aims to map the clinical decision-making process and to identify how clinicians use various factors (such as research evidence, things they know about the condition, the patient and the drug which they choose to prescribe) to reach a decision on what to prescribe first-line for a patient presenting with a first episode schizophrenia.
The primary aim of this study is to learn more about how these factors interact to contribute to the decision making process.

Do I have to take part?

Participation in this study is completely voluntary.
We are inviting all Consultant Psychiatrists and mid-grade and training grade doctors in Mental Health with experience in prescribing for schizophrenia to take part.
By agreeing to participate, you will offer an invaluable contribution to this study.

What do I have to do?

We will ask you to complete a brief questionnaire looking at factors which may (or may not) influence your prescribing behaviour.

Will my answers be kept confidential?

Your participation in the study will remain completely confidential. Your will be assigned a unique code for your questionnaire so that your data is not identifiable. No personal information is collected.
All data will be stored securely and only members of the research team will have access to the raw data. In accordance with Bangor University policy, the anonymised data will be kept for 5 years after thee conclusion of the study. It will then be destroyed.
All information used in reports, scientific papers or presentations will be anonymous.

What happens to the results of the study?

We intend to share the results of the study with healthcare professionals as well as submitting them for publication and presenting them at academic meetings and relevant conferences.
If you are interested in the findings of our study please let us know, we'll be happy to share the results.

Who has reviewed the ethics of this study?

This project has been reviewed and approved by the Bangor University Healthcare and Medical Sciences Academic Ethics Committee and the School of Psychology Research Ethics and Governance Committee.

Who can I contact for further information?

Please feel free to contact the research team if you have any questions about this project or would like further information.

Research Supervisor:
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Honorary Lecturer School of Medical Sciences,
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What if there is a problem?

If you have any study specific concerns or complaints, please contact the psychology school manager.

School Manager:
Mr. Hefin Francis
School of Psychology,
Bangor University,
Bangor, Gwynedd, LL57 2AS.
Tel: 0 1248 388339
email: h.francis@bangor.ac.uk

Thank you for taking the time to read this information sheet.

APPENDIX G

TBP Questionnaire TYPECASt study

PPT CODE: _____	SECTION 1: BACKGROUND			
A	How long have you been qualified as a psychiatrist?	1-5	6-10	Over 10 years
B	Do you routinely prescribe for schizophrenia?	Yes / No		
C	How many sessions do you work per week?			
D	Gender:	Male / Female		
E	Are you:	Consultant	Mid grade	Training grade
F	How many psychiatrists are there in your hospital?			
G	What is your approximate patient list size?			

SECTION 2: PRESCRIBING FOR PATIENTS WITH SCHIZOPHRENIA
Please list 2-3 drugs/class of drugs you prescribe routinely for schizophrenia

_____ _____ _____

1	If I prescribe these drugs, I feel that I'm doing something positive for the patient	unlikely	1	2	3	4	5	6	7	likely
2	Weight gain causes a lot of worry to the patient	unlikely	1	2	3	4	5	6	7	likely
3	If I prescribe these drugs, I will reduce positive symptoms at an early stage	unlikely	1	2	3	4	5	6	7	likely

4	In my prescribing I get to see if a drug works	unlikely	1	2	3	4	5	6	7	likely
5	The drug of my choice is not very effective	unlikely	1	2	3	4	5	6	7	likely
6	I feel rushed into making a decision without having sufficient information about a patient	unlikely	1	2	3	4	5	6	7	likely
7	The side-effects of these drugs are uncomfortable for patients	unlikely	1	2	3	4	5	6	7	likely
8	I need more information from patients to reach a diagnosis	unlikely	1	2	3	4	5	6	7	likely
9	Seeing for myself whether a drug works for a patient is	undesirable	-3	-2	-1	0	1	2	3	desirable
10	Worries and concerns expressed by patients treated with these drugs are	undesirable	-3	-2	-1	0	1	2	3	desirable
11	Doing something positive for the patient is	undesirable	-3	-2	-1	0	1	2	3	desirable
12	For the patients, reducing positive symptoms is	undesirable	-3	-2	-1	0	1	2	3	desirable
13	My experience tells me that I	should not	-3	-2	-1	0	1	2	3	should
		prescribe these drugs to patients with schizophrenia								
14	Patients with schizophrenia	disapprove	-3	-2	-1	0	1	2	3	approve
		of my prescribing these drugs to them								
15	Other psychiatrists	do not	-3	-2	-1	0	1	2	3	do
		prescribe these drugs to patients with schizophrenia								
16	NICE would	disapprove	-3	-2	-1	0	1	2	3	approve
		prescribing these drugs to patients with schizophrenia								

17	Overall I think that prescribing these drugs is		expensive	1	2	3	4	5	6	7	inexpensive
18	I feel under pressure to not prescribe expensive drugs		strongly disagree	1	2	3	4	5	6	7	strongly agree
19	I am confident that I can prescribe these drugs irrespective of the budget		strongly disagree	1	2	3	4	5	6	7	strongly agree
20	Overall, I think that prescribing these drugs to patients with schizophrenia is		unsafe	1	2	3	4	5	6	7	safe
21			efficacious	1	2	3	4	5	6	7	inefficacious
22			the wrong thing to do	1	2	3	4	5	6	7	the right thing to do
23			research evidenced	1	2	3	4	5	6	7	bad practice
24	Doing what other psychiatrists do is important to me		not at all	1	2	3	4	5	6	7	extremely
25	Following my own experience is important to me		not at all	1	2	3	4	5	6	7	extremely
26	Following NICE guidelines is important to me		not at all	1	2	3	4	5	6	7	extremely
27	The approval of my patients is important to me		not at all	1	2	3	4	5	6	7	extremely
28	I am		less likely	-3	-2	-1	0	1	2	3	more likely to prescribe these drugs to a patient if the drug is effective
29	I am		less likely	-3	-2	-1	0	1	2	3	more likely to prescribe these drugs that have side-effects to a patient
30	I am		less likely	-3	-2	-1	0	1	2	3	more likely to prescribe these drugs to a patient if I feel rushed into a decision
31	I am		less likely	-3	-2	-1	0	1	2	3	more likely

		to prescribe these drugs to a patient if I need more information about the patient									
32	People who are important to me think that I should not prescribe these drugs	strongly disagree	1	2	3	4	5	6	7	strongly agree	
33	I expect to prescribe these drugs for each patient with a typical presentation	strongly disagree	1	2	3	4	5	6	7	strongly agree	
34	I feel the social pressure to prescribe these drugs	strongly disagree	1	2	3	4	5	6	7	strongly agree	
35	I am confident that I can prescribe these drugs if I want to	strongly disagree	1	2	3	4	5	6	7	strongly agree	
36	Whether I prescribe these drugs is up to me	strongly disagree	1	2	3	4	5	6	7	strongly agree	
37	Prescribing these drugs for my patients is	easy	1	2	3	4	5	6	7	difficult	
38	I want to prescribe these drugs for my patients with schizophrenia	strongly disagree	1	2	3	4	5	6	7	strongly agree	
39	It is expected of me to prescribe these drugs to patients with schizophrenia	strongly disagree	1	2	3	4	5	6	7	strongly agree	
40	I intend to prescribe these drugs	strongly disagree	1	2	3	4	5	6	7	strongly agree	
41	Out of the next 10 patients you see with a typical diagnosis of schizophrenia, for how many patients do you expect to prescribe your preferred drug?	1	2	3	4	5	6	7	8	9	10

APPENDIX H.

TYPECASt Study data analysis - SPSS output

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