### Impact case study (REF3b)

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<tr>
<th>Institution</th>
<th>King’s College London</th>
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<td>Unit of Assessment</td>
<td>3B - Pharmacy and Nutritional Sciences</td>
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<tr>
<td>Title of case study</td>
<td>Refining Use of Psychotropic Medicines</td>
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#### 1. Summary of the impact

The use of a formulary to influence prescribing practice is common, with almost all hospitals possessing one that attempts to provide advice on the safe, effective and economic use of medicines. The Maudsley Prescribing Guidelines to Psychiatry steps beyond the function of a mere formulary and provides evidence-based guidance on the use of psychotropic medicines that influences prescribing on both a national and international basis. Now in its 11th Edition and translated into nine languages, much of the evidence in The Guidelines is generated by King’s College London research. Additionally, this research is used in other guidelines, in clinical handbooks and in prescribing practices around the world.

#### 2. Underpinning research

Pharmaceutical companies carry out clinical trials to assess the efficacy and safety of medications in a discrete group of patients under defined circumstances. More naturalistic studies taking place beyond these trials greatly extend practical knowledge of prescribing. Researchers at King’s College London (KCL) and the South London and Maudsley NHS Foundation Trust, a King’s Health Partner, including Prof David Taylor (2008-present, Chair in Psychopharmacology), Dr Maxine Patel (1999-present, Clinical Senior Lecturer) and Prof Robert Kerwin (1987-2007, Professor of Clinical Neuropharmacology), have established a reputation for undertaking research that focuses on the use of antipsychotic medicines to address some of the challenges that face prescribers on a day to day basis. They have carried out a vast number of such studies and below is an example of just a few that have made an impact.

One area of KCL research concentrates on general prescribing practices. For example, one study in 2000 looked at data from 117 centres employing psychiatric pharmacists, encompassing 3685 patients. They found that clozapine was the most commonly prescribed atypical antipsychotic and while a slight majority were given clozapine as the sole antipsychotic (56.3%), for the others, a single agent was used less often: risperidone 27.6%, sertindole 27.1%, olanzapine 18.9%, quetiapine 9.7% and amisulpride 7.1%, making co-prescribing the norm overall. Such patients co-prescribed a typical and an atypical antipsychotic were significantly more likely to be prescribed anticholinergic medication, indicating higher rates of acute extrapyramidal effects (1). Another general study looking at potential side effects by examining records from 606 hospital in-patients taking antipsychotics. Of these, 6.4% were found to have diabetes mellitus or impaired fasting glucose (DM/IFG); however, excluding these with known DM/IFG, actual prevalence in those tested in clinical practice and/or as part of this study was 16.9%. KCL researchers concluded that “in practice, clinicians should ensure that widespread, frequent testing for DM is performed” (2).

Another way KCL research has contributed to prescribing practices is by investigating the therapeutic benefit of individual antipsychotics. For instance, an examination of risperidone long-acting injection (RLAI) in 100 people with schizophrenia or schiz-affective disorder found it was well tolerated with 61% showing an improvement in Clinical Global Impressions (CGI) scale scores and antipsychotic co-prescriptions being reduced from 71% of subjects to 8% (3). Another avenue of KCL research is in guiding dosing via the use of therapeutic drug monitoring (TDM) data. For example, an audit of data from an olanzapine TDM service (n = 5856 samples) found that for dosages of 2.5-20 mg/day only 35% of results were within the suggested target range of 20-39 ng/mL. However, at doses above 20 mg/day, 30-59% of results were 60 ng/mL or greater, showing that TDM can have a role in limiting olanzapine dosage to minimize the risk of toxicity (4).

While a single medication may be viable for some, others may need combination therapy. KCL research has helped elucidate which combinations may be best to try out. An open study of 28 people resistant to clozapine found that adding amisulpride for 6 months led to significant improvement in mean scores for a number of symptom scales, with no significant changes in side effect ratings (5). However, looking at the bigger picture, in a meta-analysis encompassing 10 studies (n = 522) where clozapine had been augmented by another antipsychotic for up to 16 weeks, while augmentation showed weak but significant benefit over a placebo on either the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale, this practice showed no
advantage on CGI scores or trial withdrawal. KCL researchers concluded that clozapine augmentation may have only marginal therapeutic benefit, at least in the short term (6).

There are many antipsychotics to choose from but a person may fail to respond adequately to, stop responding to or not tolerate the first one they are prescribed. In a KCL-led study of RLAI treatment, of 211 patients followed up for 3 years, 84% discontinued. Of these, 27.7% switched to oral risperidone, which was associated with younger age, longer duration of illness and inpatient status at initiation. They concluded that outcome is likely to be improved by targeting RLAI treatment to specific patient groups (6). If a person is not doing well on a particular antipsychotic, they will need to be switched. Looking at which switching regimens may be advantageous, one 26 week, open-label, multicentre study by KCL found that effectiveness, quality of life and medication preference was greater for those switched to aripiprazole (n = 268) compared to those switched to atypical antipsychotic standard of care (SOC) treatment (olanzapine, quetiapine or risperidone) (n=254). However, while a higher proportion of patients in the SOC group had significant weight gain (21.2% vs. 7.3% for aripiprazole), the incidence of patients with one or more extrapyramidal symptom was higher in those receiving aripiprazole (13.5% vs. 5.6%) (8).

3. References to the research (indicative maximum of six references) All references are in internationally recognised, peer-reviewed journals

4. Details of the impact
Antipsychotic drug therapy is the mainstay of treatment for severe mental illnesses such as schizophrenia but prescribing is complex and optimal prescribing is hard to achieve. Findings of KCL research have informed the content of a number of country- and world-leading guidelines and been used to help guide clinical practice.

The Maudsley Prescribing Guidelines to Psychiatry
The major impact of the research described above, along with many other KCL-led studies, is inclusion in The Maudsley Prescribing Guidelines to Psychiatry (The Guidelines). This has been written by researchers at KCL and the South London and Maudsley NHS Foundation Trust since 1994 and the much-updated 11th edition was published in 2012. The Guidelines are published in
nine languages and are available in print, e-book and iPad application forms. While there are other
guides to prescribing of psychotropic medications, these are the most fully evidence-based and are
widely regarded as the leading clinical reference for all those prescribing for mental illness and
those involved in prescribing policies. Sales for the 11th edition by July 2013 were 10,500.

Individual KCL references have been used in a number of ways throughout The Guidelines. For
example, the work of Taylor 2005 on the prevalence of diabetes mellitus and impaired fasting
glucose is cited when recommending that patients’ plasma glucose should be regularly monitored.
Kerwin 2007 is used in a table describing how switching strategies, including to aripiprazole, can
be used when adverse events occur. There is also a lot of advice in The Guidelines that cites KCL
studies when focussing on individual antipsychotics. For example, Taylor 2009a is used throughout
when considering clozapine augmentation; Taylor 2000 is used when discussing co-prescribing of
typical and atypical antipsychotics and when reviewing clozapine dosing and Munro 2004 is cited
when discussing augmenting clozapine with amisulpride. Further, Patel 2011 is used to provide
evidence of how plasma level determinations of olanzapine can be utilised for those not
responding to the maximum licensed dose and recommendations for prescribing higher doses of
risperidone long-acting injection (RLAI) are evidenced by Taylor 2004 and 2009b (1).

The Guidelines are used extensively to inform clinical practice worldwide. For instance, The
International Psychopharmacology Algorithm Project is a US-led undertaking involving faculty from
several top US universities, the National Institutes of Mental Health and multiple international sites
including universities in Austria, South Africa and Japan. In an effort to improve medication choice
in psychiatry they have developed a treatment algorithm and provide a myriad of additional
information about antipsychotic regimens. Their most recent publication on this project utilises The
Guidelines throughout, especially where KCL research has been used for recommendations. For
instance, when discussing dosing and augmentation of clozapine, use of risperidone tablets and
RLAI and issues of adherence and intolerance. This project also uses individual KCL references
such as Taylor 2009a when discussing how “the evidence base supporting [clozapine]
augmentation is limited” and Patel 2011 when discussing olanzapine dosing (2).

In the UK, The Guidelines are used widely by prescribers on a daily basis, additionally, they are
cited in a number of resources, such as 2009 Leicester Partnership NHS Trust recommendations
for monitoring physical health parameters in patients prescribed antipsychotics (3). The Guidelines
are also cited in a number of clinical handbooks, just one example is ‘Polypharmacy in Psychiatry
Practice’, which cites them when discussing clozapine augmentation (4).

KCL research in UK and worldwide guidelines and beyond
The KCL research detailed above is also utilised in a number of other guidelines. In the UK, the
National Institute for Health and Care Excellence (NICE) guideline on ‘Core interventions in the
treatment and management of schizophrenia in adults in primary and secondary care’ was updated
in 2009. These guidelines dictate standard practice in England and Wales so inclusion of any
references here shows great influence. Here, Taylor 2005 is cited when discussing how people
with schizophrenia may have an increased risk of metabolic syndrome features and Taylor 2000 is
cited when discussing how prescription surveys have “confirmed a relatively high prevalence of
combined antipsychotics for people with schizophrenia” and when discussing the prevalence of
clozapine co-prescribing (5).

Recommendations of pharmacological treatment of schizophrenia produced in 2011 by the British
Association for Psychopharmacology (whose consensus group included a number of KCL
researchers) also use KCL work. They cite The Guidelines when discussing initial dosing
strategies, medication choice and using plasma monitoring to assess adherence, alongside
individual papers such as Taylor 2004 and 2009b when reviewing the use of RLAI and Taylor
2009a when considering how clozapine augmentation in treatment-resistant schizophrenia may
only be of modest benefit (6). This latter study is also used in guidelines from the 2013 Scottish
Intercollegiate Guidelines Network when it recommends that “a trial of clozapine augmentation with
a second [atypical antipsychotic] should be considered for service users whose symptoms have
not responded adequately to clozapine alone, despite dose optimisation” (7). With far wider reach,
5. Sources to corroborate the impact


2. International Psychopharmacology Algorithm Project at Harvard:
   http://www.ipap.org/welcome.php


   - Chapter 6, pgs 81-107. Antipsychotic Polypharmacy in Schizophrenia. How to Counteract This Common Practice?
   - Chapter 7, pgs 109-143. Clozapine Combinations in Treatment-Resistant Schizophrenia Patients. Lerner B, Miodownik C.


10. Munro 2004: California Department of Health Care Services:
    http://www.dhcs.ca.gov/Pages/default.aspx
    - Study of Antipsychotics Using Medi-Cal Administrative and Pharmacy Claims Data: Pg 5: