Institution: King's College London

Unit of Assessment: 3B - Pharmacy and Nutritional Sciences

Title of case study: Refining Use of Psychotropic Medicines

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 schizo-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

1. Taylor D, Mace S, Mir S, Kerwin R. A prescription survey of the use of atypical antipsychotics for hospital inpatients in the United Kingdom. Int J Psychiatry Clin Pract 2000;4(1):41-6. Doi: 10.1080/13651500052048749 (35 Scopus citations)
2. Taylor D, Young C, Mohamed R, Paton C, Walwyn R. Undiagnosed impaired fasting glucose and diabetes mellitus amongst inpatients receiving antipsychotic drugs. J Psychopharmacol 2005;19(2):182-6. Doi: 10.1177/0269881105049039 (31 Scopus citations)
3. Taylor DM, Young CL, Mace S, Patel MX. Early clinical experience with risperidone long-acting injection: a prospective, 6-month follow-up of 100 patients. J Clin Psychiatry 2004;65(8):1076-83. Doi: 10.4088/JCP.v65n0808 (42 Scopus citations)
4. Patel MX, Bowskill S, Couchman L, Lay V, Taylor D, Spencer EP, Flanagan RJ. Plasma olanzapine in relation to prescribed dose and other factors: data from a therapeutic drug monitoring service, 1999-2009. J Clin Psychopharmacol 2011;31(4):411-17. Doi: 10.1097/JCP.0b013e318221b408 (10 Scopus citations)
5. Munro J, Matthiasson P, Osborne S, Travis M, Purcell S, Cobb AM, Launer M, Beer MD, Kerwin R. Amisulpride augmentation of clozapine: an open non-randomized study in patients with schizophrenia partially responsive to clozapine. Acta Psychiatr Scand 2004;110(4):292-98. Doi: 10.1111/j.1600-0447.2004.00356.x (65 Scopus citations)
6. Taylor DM, Smith L. Augmentation of clozapine with a second antipsychotic - a meta-analysis of randomized, placebo-controlled studies. Acta Psychiatr Scand 2009a;119:419-25. Doi: 10.1111/j.1600-0447.2009.01367.x (45 Scopus citations)
7. Taylor DM, Fischetti C, Sparshatt A, Thomas A, Bishara D, Cornelius V. Risperidone long-acting injection: a prospective 3-year analysis of its use in clinical practice. J Clin Psychiatry. 2009b;70(2):196-200. Doi: 10.4088/JCP.08m04427 (16 Scopus citations)
8. Kerwin R, Millet B, Herman E, Banki CM, Lublin H, Pans M, Hanssens L, L'Italien G, McQuade RD, Beuzen JN. A multicentre, randomized, naturalistic, open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients Schizophrenia Trial of Aripiprazole: (STAR) study. Eur Psychiatry 2007;22(7):433-43. Doi: 10.1016/j.eurpsy.2007.03.002 (63 Scopus citations)

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,

the World Federation of Societies of Biological Psychiatry, a non-profit organisation representing professionals from over 70 countries, produces guidelines on schizophrenia treatment. These use information from Kerwin 2007 to confirm the effectiveness of aripiprazole (8). KCL research has also been used in a number of clinical handbooks. For instance, Munro 2004 is cited when discussing evidence that clozapine can be augmented with amisulpride in the book 'Novel Antischizophrenia Treatments' (9) and both this study and Taylor 2009a are also cited in the book 'Polypharmacy in Psychiatry Practice' (2).

Beyond books and guidelines, KCL research has been used for practical purposes. For instance, the California Mental Health Care Program produce a quarterly report on antipsychotic use with the aim to improve the quality of services involved in mental health care in California. Here they cite Munro 2004 when discussing co-prescribing of clozapine and amisulpride (10).

5. Sources to corroborate the impact

1. The Maudsley Prescribing Guidelines in Psychiatry. Eleventh Edition. Taylor D, Paton C, Kapur S. Wiley-Blackwell 2012. ISBN 978-0-470-97948-8. Pgs 6, 28, 31, 44, 52, 66, 67, 84, 85, 487: http://www.kcl.ac.uk/iop/mentalhealth/publications/guidelines.aspx
2. International Psychopharmacology Algorithm Project at Harvard: http://www.ipap.org/welcome.php.
   - Osser DN, Roudsari MJ, Manschreck T. The psychopharmacology algorithm project at the Harvard South Shore Program: an update on schizophrenia. Harv Rev Psychiatry 2013;21(1):18-40 (pgs 26, 28, 30). Doi: 10.1097/HRP.0b013e31827fd915
3. Leicester Partnership NHS Trust: Guidelines to monitoring of physical health parameters in patients with serious mental illness prescribed regular antipsychotics. 2009 (pg 5): http://www.leicspart.nhs.uk/Library/PhysicalParameterMonitoringinPatientsonAntipsychoticsSept2012MHLDPG.pdf
4. Polypharmacy in Psychiatry Practice, Volume II. Use of Polypharmacy in the "Real World." Ritsner MS (Ed). Springer 2013. ISBN: 978-94-007-5798-1: http://link.springer.com/book/10.1007/978-94-007-5799-8
   - 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.
5. Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (updated edition). National Clinical Guideline Number 82. 2009/10 (pgs 100, 125): http://www.nice.org.uk/nicemedia/live/11786/43607/43607.pdf
6. Barnes TRE and the Schizophrenia Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2011;25(5):567-620 (pgs 571, 574, 575, 580, 581, 588, 594. Doi: 10.1177/0269881110391123
7. Scottish Intercollegiate Guidelines Network. SIGN 131. Management of schizophrenia (p20), 2013: http://www.sign.ac.uk/pdf/sign131.pdf
8. Hasan A, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry 2012;13(5):318-78 (pg 336). Doi: 10.3109/15622975.2012.696143
9. Novel Antischizophrenia Treatments. Series: Handbook of Experimental Pharmacology, 2012 Vol. 213 Geyer, Mark A.; Gross, Gerhard (Eds.) Chapter 7, pp 167-210. The Role of Dopamine D3 Receptors in Antipsychotic Activity and Cognitive Functions. Gross G, Drescher K. Springer. ISBN 978-3-642-25758-2: http://www.springer.com/biomed/pharmacology+%26+toxicology/book/978-3-642-25757-5
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: http://www.dhcs.ca.gov/provgovpart/Documents/CalMEND/URUM%20Reports/URUM%20Report%20OctMarch10.pdf