*Irish Journal of Psychological Medicine* (2014), **31**, 167–173. 
doi:10.1017/ipm.2014.18

ORIGINAL RESEARCH

# The impact of a change in prescribing policy on antipsychotic prescribing in a general adult psychiatric hospital

**J. Kelly[1,*], F. Kelly[2,*], K. Santlal[3] and S. O'Ceallaigh[4]**

[1] *Psychiatry Lecturer, Department of Psychiatry, Cork University Hospital, Dublin, Ireland*
[2] *Clinical Lecturer, Trinity College & Senior Registrar, Our Lady's Hospital Navan, Dublin, Ireland*
[3] *Registrar, St. Patrick's University Hospital, Dublin, Ireland*
[4] *Consultant Psychiatrist, St. Patrick's University Hospital, Dublin, Ireland, Ireland*

**Objectives.** To examine the impact of a change in local prescribing policy on the adherence to evidence-based prescribing guidelines for antipsychotic medication in a general adult psychiatric hospital.

**Methods.** All adult in-patients had their clinical record and medication sheet reviewed. Antipsychotic prescribed, dose prescribed and documented indications for prescribing were recorded. This was done before and after the implementation of the change in hospital antipsychotic prescribing policy.

**Results.** There were no significant differences in age, sex, Mental Health Act status, psychiatric diagnosis or documented indications for prescribing multiple or high dose antipsychotics between the two groups. There was an increase in the preferential prescribing of multiple second-generation antipsychotics ($p = 0.01$) in the context of a significant reduction in the prescribing of multiple antipsychotics overall ($p = 0.02$). There were no significant reductions in prescribing of mixed generations of antipsychotics ($p = 0.12$), high dose antipsychotics ($p = 1.00$) or as required (PRN) antipsychotics ($p = 0.74$).

**Conclusions.** Changes in local prescribing policy can improve adherence to quality prescribing guidelines and cause clinically significant improvements in patterns of prescribing in a general adult psychiatric hospital.

*Received 30 January 2014; Revised 30 March 2014; Accepted 14 April 2014; First published online 9 May 2014*

**Key words:** Antipsychotic agents, clinical audit, inappropriate prescribing, physician prescribing patterns, schizophrenia.

## Introduction

Antipsychotics are effective at reducing the risk of relapse in schizophrenia at 1-year follow-up (Leucht *et al.* 2012). The practice of prescribing multiple and high dose antipsychotics is common (Faries *et al.* 2005), not supported by the evidence base (Goren *et al.* 2008; Goodwin *et al.* 2009; CADTH 2012; Donnelly *et al.* 2013) and is associated with increased side effects and cost (Lochmann van Bennekom *et al.* 2013). While several studies report a reduction in all-cause mortality in schizophrenic patients prescribed antipsychotic medication (Tiihonen *et al.* 2009) the rate of cardiac mortality is higher than among those not prescribed antipsychotics and increases with higher doses (Ray *et al.* 2009). As required (PRN) prescribing was identified as a major cause of both high dose and combined antipsychotic prescribing (Paton *et al.* 2008) and occurs in up to half of psychiatric in-patients (Fishel *et al.* 1994).

Evidence-based guidelines recommend commencing monotherapy at the lower end of the licensed dose range and titrating upwards within the dose range (NICE 2009). Switching from combined antipsychotic therapy to monotherapy is a viable option for those who do not have refractory schizophrenia and can reduce side effects (Essock *et al.* 2011; Tani *et al.* 2013). In a study by Wunderink *et al.* (2013) dose reduction when in remission can result in better long term functional outcomes, including self-care, relationships, community integration and vocational functioning as measured by the Groningen Social Disability Schedule. A meta-analysis of 14 studies ($N = 734$) investigating clozapine augmentation with antipsychotics in patients with treatment-resistant schizophrenia demonstrated a modest benefit compared with augmentation with placebo (Taylor *et al.* 2012).

A Prescribing Observatory for Mental Health United Kingdom (POMH-UK) audit carried out in 2006 and 2007 involving 32 services in the United Kingdom and Ireland found little change in the rates of multiple, high dose and PRN antipsychotic prescribing in the majority

* J. Kelly and F. Kelly are joint first co-authors.
Address for correspondence: J. Kelly, Psychiatry, Cork University Hospital, Psychiatry Department, Cork University Hospital, Cork, Co. Cork, Ireland.
(Email: kellyjr@tcd.ie)

of services, after the introduction of a wide array of different quality improvement programmes (Paton *et al.* 2008). These included, but were not limited to, a benchmarked audit report, electronic slide presentation, educational work book, antipsychotic dose ready reckoner, time series chart that enabled clinical staff to chart their use of multiple antipsychotics and high dose antipsychotics over time so that trends could be identified, educational posters, workshops and various combinations thereof.

### *Standards set for audit*

The standards set were the evidence-based guidelines underpinning the POMH-UK audit of 2006–2007 (Paton *et al.* 2008) that were derived from the following sources: National Institute of Health and Care Excellence guidelines (NICE 2009), British National Formulary (BNF) (Joint Formulary Committee, BMA, RPSOGB 2012) and the Royal College of Psychiatry guidelines (RCPSYCH 2006).

The POMH-UK audit standards for adherence to quality prescribing guidelines are as follows:

1. The total daily prescribed doses of antipsychotic drugs are within BNF/Summary of Product Characteristics limits. High dose is defined as a total daily dose, exceeding 100% of the maximum recommended daily dose (RCPSYCH 2006).
2. Individuals should be prescribed only one antipsychotic at a time with the exception of cross titration during switching from one antipsychotic to another and those requiring augmentation of clozapine (NICE 2009).
3. First (typical) and second-generation (atypical) antipsychotic drugs (SGAs) should not be prescribed concurrently, except during switching from one generation to another (NICE 2009).

### *Ethical approval*

The audit was approved by the St Patrick's and St Edmundsbury's Hospitals' Audit Committee.

## Methods

Over a 4-day period in 2008 all adult in-patients ($N = 281$) had their medication sheet and clinical record separately reviewed by two independent investigators. Of these, 161 patients were prescribed regular and/or PRN antipsychotic medication. The following information was gathered for any patient prescribed antipsychotic medication: age, gender, ICD 10 diagnosis code, Mental Health Act status, medication name, dose, frequency and generation of antipsychotic prescribed. If multiple and/or high dose antipsychotics were prescribed any reasons documented for this prescribing were recorded.

The protocol established by POMH-UK their 2006 and 2007 audit of antipsychotic prescribing in mental health facilities was followed (RCPSYCH 2006). This included:

- The maximum prescribed dose that could be administered over a 24 hours period was recorded, for both regular and PRN prescriptions, irrespective of whether they were administered or not.
- The dose of each antipsychotic medication was compared with the BNF maximum licensed dose.
- The percentages were summed to determine the total daily antipsychotic dose percentage that could be given in 24 hours (Paton *et al.* 2008).

Over a 2-day period in June 2012, an identical data-gathering process was repeated for all adult in-patients ($N = 239$). Of these 131 patients were prescribed regular and/or PRN antipsychotic medication. This data was separately reviewed by two independent investigators and a consensus meeting, involving a senior colleague, held to resolve any disagreements.

In 2008 two patients prescribed clozapine were augmented by regularly prescribed antipsychotics, one first generation and one second generation. In 2012, three patients were prescribed clozapine augmented with regularly prescribed antipsychotics, two of which were second generation and one first generation. All of the patients prescribed clozapine and regular antipsychotics as augmenting agents were excluded as per the POMH-UK audit standards.

Data collected was analysed using SPSS 20.0. $\chi^2$ testing and cross tabulation were used to determine statistical significance.

### *Intervention*

The intervention, implemented in December 2011, consisted of a hospital-wide clinical policy titled 'Prescribing and monitoring of antipsychotic medication, including high dose antipsychotic medication' (SPUH 2011).

The primary objectives of the policy were that:

- Treatment with antipsychotic medication should be as effective, safe and as well tolerated as possible.
- Treatment with antipsychotic medication should consider patient preference and relative potential of antipsychotics to cause extrapyramidal side effects, metabolic side effects and other side effects.
- Concurrent use of two or more antipsychotics should be avoided where possible, in particular the use of first generation and second generation in combination.

Additional guidelines for high dose antipsychotic treatment (HDAT) included that:

- The decision to prescribe HDAT should be made by the consultant psychiatrist and documented in the clinical

https://doi.org/10.1017/ipm.2014.18 Published online by Cambridge University Press

notes, including the clinical justification for this decision, the risks, benefits and assessment of outcomes.
- A sheet monitoring physical observations and baseline and ongoing investigations was introduced for patients on high dose antipsychotics.

All departments – pharmacy, nursing, consultant hospital doctors and non-consultant hospital doctors (NCHD) – were involved in creating, disseminating and implementing the policy throughout the organisation. All staff were made aware of the new policy through email contact, formalised staff training sessions, informal discussion during multi-disciplinary team (MDT) meetings, pharmacy-led interventions during ward rounds and MDT meetings and during induction training for new staff. In addition the policy was available both on the wards and via the organisation's intranet. The policy was included in NCHD induction and presented at the NCHD weekly educational meetings. Educational sessions were also held for all MDT members.

## Results

In 2008, 161 of 281 in-patients were prescribed antipsychotic medication compared with 131 of 239 in-patients in 2012 ($p = 0.60$). There were no significant differences in age, gender, Mental Health Act status, psychiatric diagnosis or documented indications for prescribing multiple or high dose antipsychotics between the two groups. The number of patients prescribed multiple antipsychotics decreased from 45 of 161 patients prescribed antipsychotic medication in 2008 to 21 of 131 patients prescribed antipsychotic medication in 2012 ($p = 0.02$).

The prescribing of multiple first-generation antipsychotics (FGAs) including PRN's decreased from 5 of 45 patients prescribed multiple antipsychotics in 2008 to 0 of 21 prescribed multiple antipsychotics including PRN's in 2012 ($p = 0.17$). In 2008, 11 patients were prescribed multiple SGAs including PRN's out of 45 compared with 12 out of 21 prescribed multiple SGAs including PRN's in 2012 ($p = 0.01$) (Fig. 1).

There was a decrease in the prescribing of mixed generations of antipsychotics from 29 of 45 patients in 2008 to 9 of 21 patients in 2012 ($p = 0.12$). The rate of high dose antipsychotic prescribing remained stable at 13 of 161 patients in 2008 and 10 of 131 in 2012 ($p = 1.00$) (Fig. 1).

The number of patients prescribed a PRN antipsychotic fell from 25 of 161 patients prescribed antipsychotic medication in 2008 compared with 18 of 131 patients prescribed antipsychotic medication in 2012 ($p = 0.74$). Fourteen of the 45 patients prescribed multiple antipsychotics in 2008 were prescribed PRN antipsychotics. This fell to 6 of 21 patients prescribed multiple antipsychotics in 2012 ($p = 1.00$). Seven of 13 patients prescribed high dose antipsychotics in 2008 were prescribed a PRN antipsychotic while 2 of 10 patients prescribed high dose antipsychotics in 2012 were prescribed a PRN antipsychotic ($p = 0.20$) (Fig. 2).

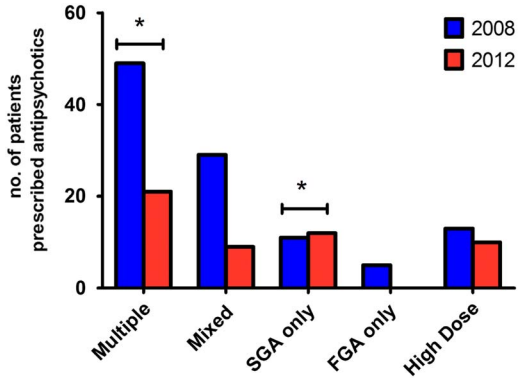


**Fig. 1.** Multiple antipsychotic prescribing 2008 and 2012. *$p < 0.05$. FGA, first-generation antipsychotics; SGA, second generation antipsychotics.

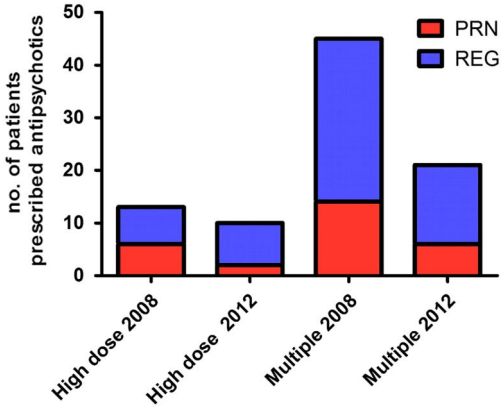


**Fig. 2.** PRN contribution to high dose and multiple antipsychotic prescribing (2008 and 2012).

In 2008, of the 20 patients diagnosed as having a psychotic disorder (F20–29), 12 were prescribed multiple antipsychotics while in 2012, 2 of 18 patients diagnosed with a psychotic disorder were prescribed multiple antipsychotics ($p < 0.01$). In 2008, 5 out of 13 patients prescribed high dose antipsychotics were diagnosed with a psychotic disorder compared with none of the 10 prescribed high dose antipsychotics in 2012 ($p = 0.05$).

Of the 97 patients diagnosed as having a mood disorder (F30–39) in 2008, 23 were prescribed multiple antipsychotics compared with 16 of 81 prescribed multiple antipsychotics in 2012 ($p = 0.06$). In 2008, 6 of 13 patients prescribed high dose antipsychotics were diagnosed as having mood disorders (F30–39) compared with 7 of 10 patients prescribed high dose antipsychotics in 2012 ($p = 0.40$).

https://doi.org/10.1017/ipm.2014.18 Published online by Cambridge University Press

## Discussion

The CATIE (Lieberman *et al.* 2005) and CUtLASS (Jones *et al.* 2006) trials challenged the concept that SGAs were superior to FGAs in terms of symptom reduction and improved quality of life. The World Psychiatric Association's review of 1600 randomised controlled trials concluded that SGA's had a lower propensity to cause extrapyramidal side effects and tardive dyskinesia, though greater propensity to result in metabolic side effects (Tandon *et al.* 2008). Excluding clozapine, which has consistently been shown to be the most effective antipsychotic (Leucht *et al.* 2013), there are minimal differences between FGAs and SGAs in treating positive symptoms (Abou-Setta *et al.* 2012, Rosenheck & Lin 2014).

The classification of antipsychotics into FGA and SGA groups may be an oversimplification and it has been proposed that this distinction be rejected (Tyrer & Kendall 2009). A meta-analysis of 212 trials, by Leucht *et al.* suggest that instead of grouping antipsychotics into FGA and SGA, hierarchies in different domains, such as all-cause discontinuation, weight gain, extrapyramidal side effects, prolactin increase, QTc prolongation and sedation, would be more useful in determining the optimal antipsychotic for an individual (Leucht *et al.* 2013). Notwithstanding this since the POMHS-UK Guidelines (Paton *et al.* 2008) used this classification we also utilised it as the basis for classifying antipsychotic medications in this study.

The primary mechanism of action of FGAs and SGAs in the treatment of positive symptoms is D2/3 striatal receptor blockade, with a threshold D2 receptor occupancy of 65% needed for response, and an increased risk of side effects with D2 occupancy greater than 80% (Howes *et al.* 2009). Combining two antipsychotics with high affinity for D2/3 blockade may result in an increased risk of side effects. The combination of a low potency antagonist like clozapine or quetiapine with a high affinity D2/3 blocker may be logical however, at this point, clear evidence is lacking (Goodwin *et al.* 2009). Clozapine has less affinity for D2 receptors, blocking ~30–50%, and has less propensity to cause EPSE's (Kane 2008), though the precise mechanism for its superior efficacy is not fully known (Stone *et al.* 2010). A meta-analysis of 14 studies investigating clozapine augmentation with a second antipsychotic demonstrated a small reduction in symptom scores compared with augmentation with a placebo (Taylor *et al.* 2012), though there is little evidence to demonstrate that, excluding co-prescribing with clozapine, multiple antipsychotic prescribing is an effective treatment strategy (Kane *et al.* 2009). Despite this, multiple antipsychotic prescribing occurs in up to 15–20% of patients with schizophrenia (Edlinger *et al.* 2005; Patel *et al.* 2014).

The principal finding of this study was the reduction in the prescribing of multiple antipsychotics after a change in local prescribing guidelines. The rate of multiple antipsychotic prescribing among all in-patients prescribed an antipsychotic medication fell from 27% pre-intervention to 16% post-intervention compared with 43% in 2006 and 39% in 2007 in the Paton *et al.* study. In this study, mixed generation antipsychotics were prescribed in 64% of patients prescribed multiple antipsychotics pre-intervention compared with 42% post-intervention. Paton *et al.* reported rates of mixed generation antipsychotic prescribing of 31% of those prescribed antipsychotics pre-intervention and 29% post-intervention. The elimination of multiple FGA prescribing contributed to the decrease in prescribing of multiple antipsychotics. While multiple antipsychotic prescribing was reduced, there was a shift to prescribing multiple SGAs that increased from 6.8% of all antipsychotics prescribed in 2008 to 9.2% in 2012. This pattern mirrors a general shift from FGA to SGA prescribing (Donohue *et al.* 2014).

Up to 10% of schizophrenic patients are prescribed high doses, despite lack of evidence and increased risk of side effects (Patel *et al.* 2014). In the Paton *et al.* study high dose prescribing was 36% in 2006 and 34% in 2007 (Paton *et al.* 2008). In this study the rate of high dose antipsychotic prescribing was 7% at baseline and 8% post-intervention. Although the proportion of patients prescribed high dose antipsychotics was significantly less in this study, the rate of high dose prescribing remained unchanged post-intervention. This may have implications for risk of side effects and, in conjunction with multiple antipsychotic prescribing, may result in delays to commencing evidence-based clozapine treatment (Howes *et al.* 2012, Agid *et al.* 2013) in the one-third of patients that may be treatment resistant (NICE 2009).

This study demonstrated a marked reduction in the prescribing of multiple and high dose antipsychotics in patients diagnosed with psychotic disorders (F20–29), however reductions in multiple and high dose prescribing were not significant in patients diagnosed with mood disorders (F30–39). This is an area where a more targeted intervention could be directed.

While PRN antipsychotic medication prescribing rates were higher in Paton *et al.*'s study than the 15% rate in this study, the rate of prescribing did not change significantly in either study following intervention. It continues to be an important factor for non-adherence to antipsychotic prescribing guidelines and a more targeted intervention may yield significant benefits in future.

Overall, Paton *et al.* found little difference in adherence to guidelines following the introduction of a wide

https://doi.org/10.1017/ipm.2014.18 Published online by Cambridge University Press

range of interventions. They proposed three reasons for interventions failing:

- The standards might not have been accepted by clinicians.
- The interventions may not have reached or been acceptable to clinicians.
- Cultural or organisational factors may have impeded change in each institution (Paton *et al.* 2008).

Tani *et al.* highlighted that passive interventions were less effective compared with active educational interventions that directly cautioned doctors on the use of combined and high dose antipsychotic prescribing (Tani *et al.* 2013). The success of the intervention in this study in effecting change may be accounted for by the following factors:

1. The policy was mentioned during compulsory induction and each new NCHD received a copy of policy at induction.
2. All departments agreed to implement the intervention.
3. The policy was widely accepted and seen to be beneficial by clinicians.
4. The Pharmacy Department were active in continuing to promote adherence to the policy via reminders at ward rounds and MDT meetings.

### *Limitations*

Information regarding which doctors prescribed the antipsychotics was not gathered in this study. This prevents us from identifying any differences in prescribing practice among teams within the hospital before and after the intervention and also prevents us from drawing any conclusions as to whether the changes in prescribing practice found occurred in all teams or were concentrated within a subset of them.

It is possible that a concomitant policy change prohibiting PRN benzodiazepine prescribing by NCHDs may have caused a shift to PRN antipsychotic prescribing instead of PRN benzodiazepine prescribing. The significant change to benzodiazepine prescribing policy at the same time within the organisation acts as a confounder to making it impossible to state that the changes were solely due to the change in antipsychotic prescribing policy. Benzodiazepine and other psychotropic medication prescribing was not recorded and this limits the study's ability to account for their impact on the results of the study.

Data regarding diagnosis was gathered and analysed using ICD 10 coding groups, rather than the precise diagnosis code, therefore limiting more detailed analysis of diagnosis and antipsychotic prescribing.

This study took place in a non-for-profit hospital in which change may be easier to implement than within the HSE due to differences in scale, unionisation and organisation. This may limit the generalisability of the study.

## Conclusion

This audit showed that implementation of a new hospital-wide antipsychotic prescribing policy, which engages with all departments and clinicians through a concerted, targeted, ongoing educational campaign can positively impact on practice improving adherence to quality prescribing guidelines.

### *Recommendations*

It would be beneficial to re-audit on an ongoing basis to ensure there is a sustained improvement in antipsychotic prescribing adherence to guidelines. The incorporation of an educational intervention into the NCHD induction programme to improve knowledge of and adherence to prescribing guidelines may help increase quality prescribing. We would also welcome additional centres to carry out similar research in order to examine the generalisability of these findings.

## Acknowledgements

We acknowledge the contribution of Ms Margaret Nichol, Clinical Audit Facilitator, and St. Patrick's University Hospital.

## References

**Abou-Setta AM, Mousavi SS, Spooner C, Schouten JR, Pasichnyk D, Armijo-Olivo S, Beaith A, Seida JC, Dursun S, Newton AS, Hartling L** (2012). First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness. Comparative Effectiveness Review No. 63. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2007-10021). AHRQ Publication No. 12-EHC054-EF. Rockville, MD: Agency for Healthcare Research and Quality; www.effectivehealthcare.ahrq.gov/reports/final.cfm.

**Agid O, Schulze L, Arenovich T, Sajeev G, Mcdonald K, Foussias G, Fervaha G, Remington G** (2013). Antipsychotic response in first-episode schizophrenia: efficacy of high doses and switching. *European Neuropsychopharmacology* **23**, 1017–1022.

**CADTH** (2012). Combination and high-dose atypical antipsychotic therapy in patients with schizophrenia: systematic review. *CADTH Technology Overviews* **2**, e2301.

**Donnelly L, Rathbone J, Adams CE** (2013). Haloperidol dose for the acute phase of schizophrenia. *Cochrane Database of Systematic Reviews* **8**, CD001951.

**Donohue J, O'malley AJ, Horvitz-Lennon M, Taub AL, Berndt ER, HUSKAMP HA** (2014). Changes in physician antipsychotic prescribing preferences, 2002–2007. *Psychiatric Services* **65**, 315–322.

https://doi.org/10.1017/ipm.2014.18 Published online by Cambridge University Press

**Edlinger M, Hausmann A, Kemmler G, Kurz M, Kurzthaler I, Walch T, Walpoth M, Fleischhacker WW** (2005). Trends in the pharmacological treatment of patients with schizophrenia over a 12 year observation period. *Schizophrenia Research* **77**, 25–34.

**Essock SM, Schooler NR, Stroup TS, Mcevoy JP, Rojas I, Jackson C, Covell NH** (2011). Effectiveness of switching from antipsychotic polypharmacy to monotherapy. *American Journal of Psychiatry* **168**, 702–708.

**Faries D, Ascher-Svanum H, Zhu B, Correll C, Kane J** (2005). Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics. *BMC Psychiatry* **5**, 26.

**Fishel AH, Ferreiro BW, Rynerson BC, Nickell M, Jackson B, Hannan BD** (1994). As-needed psychotropic medications: prevalence, indications, and results. *Journal of Psychosocial Nursing and Mental Health Services* **32**, 27–32.

**Goodwin G, Fleischhacker W, Arango C, Baumann P, Davidson M, de Hert M, Falkai P, Kapur S, Leucht S, Licht R, Naber D, O'keane V, Papakostas G, Vieta E, Zohar J** (2009). Advantages and disadvantages of combination treatment with antipsychotics ECNP Consensus Meeting, March 2008, Nice. *European Neuropsychopharmacology* **19**, 520–532.

**Goren JL, Parks JJ, Ghinassi FA, Milton CG, Oldham JM, Hernandez P, Chan J, Hermann RC** (2008). When is antipsychotic polypharmacy supported by research evidence? Implications for QI. *Joint Commission Journal on Quality and Patient Safety* **34**, 571–582.

**Howes OD, Egerton A, Allan V, Mcguire P, Stokes P, Kapur S** (2009). Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. *Current Pharmaceutical Design* **15**, 2550–2559.

**Howes OD, Vergunst F, Gee S, Mcguire P, Kapur S, Taylor D** (2012). Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *British Journal of Psychiatry* **201**, 481–485.

**Joint Formulary Committee, British Medical Association, Royal Pharmaceutical Society of Great Britain** (2012). British National Formulary (BNF) March 2012, Edited by Joint Formulary Committee, Pharmaceutical Press, London.

**Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW** (2006). Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). *Archives of General Psychiatry* **63**, 1079–1087.

**Kane JM** (2008). An evidence-based strategy for remission in schizophrenia. *Journal of Clinical Psychiatry* **69** (Suppl. 3): 25–30.

**Kane JM, Correll CU, Goff DC, Kirkpatrick B, Marder SR, Vester-Blokland E, Sun W, Carson WH, Pikalov A, Assuncao-Talbott S** (2009). A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. *Journal of Clinical Psychiatry* **70**, 1348–1357.

**Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, SAMARA M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lassig B, Salanti G, Davis JM** (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* **382**, 951–962.

**Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM** (2012). Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database of Systematic Reviews* **5**, CD008016.

**Lieberman JA, Stroup TS, Mcevoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK** (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine* **353**, 1209–1223.

**Lochmann van Bennekom MW, Gijsman HJ, Zitman FG** (2013). Antipsychotic polypharmacy in psychotic disorders: a critical review of neurobiology, efficacy, tolerability and cost effectiveness. *Journal of Psychopharmacology* **27**, 327–336.

**National Institute for Health and Clinical Excellence (NICE)** (2009). *Schizophrenia. Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care*. London (UK): National Institute for Health and Clinical Excellence (NICE); March 2009, 41p. (NICE clinical guideline; no. 82).

**Patel MX, Bishara D, Jayakumar S, Zalewska K, Shiers D, Crawford MJ, Cooper SJ** (2014). Quality of prescribing for schizophrenia: evidence from a national audit in England and Wales. *European Neuropsychopharmacology* **24**(4), 499–509.

**Paton C, Barnes TR, Cavanagh MR, Taylor D, Lelliott P** (2008). High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. *British Journal of Psychiatry* **192**, 435–439.

**Ray WA, Chung CP, Murray KT, Hall K, Stein CM** (2009). Atypical antipsychotic drugs and the risk of sudden cardiac death. *New England Journal of Medicine* **360**, 225–235.

**RCPSYCH** (2006). Consensus statement on the use of high-dose antipsychotic medication, Council Report CR138, Royal College of Psychiatrists.

**Rosenheck R, Lin H** (2014). Noninferiority of perphenazine vs. three second-generation antipsychotics in chronic schizophrenia. *Journal of Nervous and Mental Disease* **202**, 18–24.

**SPUH** (2011). Prescribing and monitoring of antipsychotic medication including high dose antipsychotic medication. Policy No. CLIN 0007.

**Stone JM, Raffin M, Morrison P, Mcguire PK** (2010). Review: the biological basis of antipsychotic response in schizophrenia. *Journal of Psychopharmacology* **24**, 953–964.

**Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ JR, Okasha A, Singh B, Stein DJ, Olie JP, Fleischhacker WW, Moeller HJ** (2008). World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophrenia Research* **100**, 20–38.

**Tani H, Uchida H, Suzuki T, Fujii Y, Mimura M** (2013). Interventions to reduce antipsychotic polypharmacy: a systematic review. *Schizophrenia Research* **143**, 215–220.

https://doi.org/10.1017/ipm.2014.18 Published online by Cambridge University Press

**Taylor DM, Smith L, Gee SH, Nielsen J** (2012). Augmentation of clozapine with a second antipsychotic – a meta-analysis. *Acta Psychiatrica Scandinavica* **125**, 15–24.

**Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J** (2009). 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* **374**, 620–627.

**Tyrer P, Kendall T** (2009). The spurious advance of antipsychotic drug therapy. *Lancet* **373**, 4–5.

**Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ** (2013). Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry* **70**(9), 913–920.

https://doi.org/10.1017/ipm.2014.18 Published online by Cambridge University Press