Reviewer's report

Title: Antipsychotic polypharmacy in a regional health service: a population-base study

Version: 2 Date: 21 April 2011

Reviewer: James Karagianis

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Review of antipsychotic polypharmacy paper for BMC psychiatry, April 20, 2011

1. Is the question posed by the authors well-defined? Yes.

2. Are the methods appropriate and well described? Somewhat, but methodology limitations have prevented providing a better answer to the question.

3. Are the data sound? Probably.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes except for the absence of any statistical methodology.

5. Are the discussions and conclusions well-balanced and adequately supported by the literature? Fairly reasonable.

6. Are the limitations of the work clearly stated? Some are, and some aren’t. The limitations of lack of diagnosis and dose information are acknowledged, but the impact of these limitations are not given enough emphasis. Also the limitation of the absence of any statistical comparison is not acknowledged.

7. Do the authors acknowledge any work upon which they are building, both published and unpublished? Yes, but they have missed at least two other articles that may be relevant in discussing polypharmacy in a community setting. The 2-year Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS), a large open-label observational study of treatment outcomes of 448 clinically stable patients with schizophrenia, reported a prevalence of polypharmacy at 15.6% in outpatients treated at academic and community-based clinics (Williams R, Kopala L, Malla A, et al. Medication decisions and clinical outcomes in the Canadian National Outcomes Measurement Study in Schizophrenia. Acta Psychiatr Scand 2006;113(Suppl. 430):12-21). The Health Outcomes of a Canadian Community Cohort found a prevalence of antipsychotic polypharmacy of around 50% in a cohort of outpatients needing a change in treatment for schizophrenia. (Antipsychotic switching: results from a one-year prospective, observational study of patients with schizophrenia. Karagianis J, Williams R, Davis L, Hanley JB, Chandrasena R, Thakur A and Dickson R. Current Medical Research and Opinion 2009; 25 (9):2121-32). Other potentially relevant papers include


8. Do the title and abstract accurately convey what has been found? Yes.

9. Is the writing acceptable? Yes.

The authors have written an interesting paper which addresses an important topic and is a worthwhile contribution to the body of scientific knowledge.

Major Compulsory Revisions

The description of Criterion 3 is unclear. For example, does filter 2 mean more than one package of each drug was dispensed in the fourth month prior? There seems to be an assumption that dispensing occurs monthly, but that may not be the case and the criteria may be applied differently if the medications are dispensed weekly for example. My main concern is that the criteria do not distinguish clearly between sequential use and simultaneous use of more than one antipsychotic. If this can be clarified, that would help, but if not, it needs to be acknowledged as a limitation.

Illness severity of the population under study should be discussed. The guidelines would reserve polypharmacy for specific situations, such as treatment refractory illness, but there is no mention of any measure of illness severity in their study population, or the absence of this as a limitation.

Minor Essential Revisions

In order to provide a better answer to the main question, the authors should be more explicit about exactly what the guidelines say regarding polypharmacy, as opposed to just paraphrasing. For example, if there are limitations on the use of antipsychotic polypharmacy, what are those limitations specifically? Also, since the patients are heterogeneous, the authors should also cover guidelines for other disorders that use antipsychotics, such as bipolar disorder.

Risperidone LAI is intended to be used with a period of overlap with an oral antipsychotic. This could potentially be counted as antipsychotic polypharmacy, and the authors should mention whether this would be included or excluded.

The authors need to address the lack of statistical comparisons in this manuscript, which may further limit conclusions that can be drawn. They say in the methods that statistical analysis was performed using SPSS, but no significance is given for any of their comparisons.

The authors should briefly discuss the implications of each of the limitations

Discretionary Revisions

In introducing their study, the authors mentioned safety and lack of evidence of
benefit, but they should also mention the other common reason for discouraging polypharmacy, the additional cost.

The manuscript discusses the relatively low use of clozapine compared to another study of severe schizophrenia. The other point worth making here is that since this study was not limited to schizophrenia, and clozapine is only indicated in schizophrenia, the denominator is bound to be larger here than in a study of pure schizophrenia. This is in addition to the severity issue.

The authors should also comment on the wisdom of using depots combined with oral agents. The purpose of a depot is usually to ensure adherence, so it seems counterintuitive to add an oral medication, since the patient was assumed to not be reliably taking oral medications. This could be an argument for the futility of such combinations.

The authors should acknowledge that there is a great potential for off label use in their sample, and caution readers against drawing conclusions that this is a paper about polypharmacy in schizophrenia, or about differences in individual drugs.

The authors have acknowledged that the majority of prescriptions in the region occur within the system they studied, but it would be very informative to know roughly what percent of prescriptions are written by doctors outside of the Catalan National Health Service and for inpatients.

The first paragraph on page 15 is essentially a repeat of statements made on page 11, and can be deleted.

There is other relevant literature that could be cited in the introduction or discussion, listed above.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I am a clinical research physician employed by Eli Lilly USA, responsible for Zyprexa and Symbyax. I own shares of Eli Lilly. Publication or rejection of this paper is unlikely to have any impact on the sales of Zyprexa or the price of Lilly stock. I am the lead author of one of the papers I have suggested for citation because of its relevance to the issue of polypharmacy prevalence. I have no other competing interests to declare.