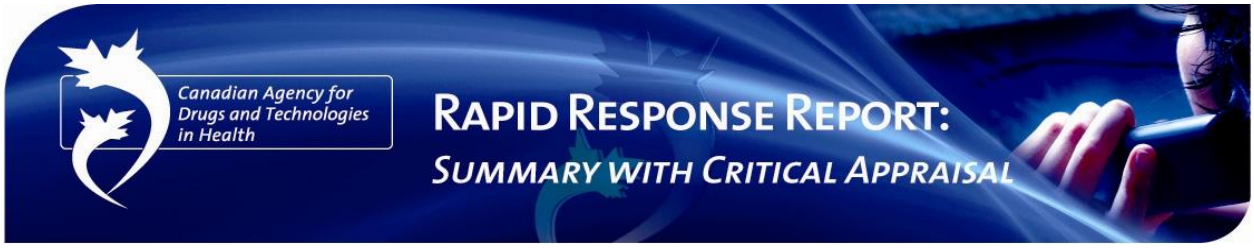

TITLE: Amisulpride for Adults with Refractory Schizophrenia: A Review of the Clinical Effectiveness and Safety

DATE: 3 June 2011

CONTEXT AND POLICY ISSUES

Schizophrenia is characterized by recurrent or chronic episodes of psychosis, with progressive clinical and functional deterioration over time.[1] Symptoms include delusions, hallucinations and disorganized or chaotic thinking and behaviour.[1] These symptoms affect the individual's ability to function in many dimensions of life, including school, work, social functioning and personal care.[1] At some point in their lives, approximately 0.6% of the population will be affected by schizophrenia.[1]

Pharmacotherapy with antipsychotics is considered a mainstay of treatment of schizophrenia.[2] Antipsychotic medications can be categorized as typical or first generation and atypical or second generation.[3] Second generation antipsychotics have largely replaced the first generation agents in the management of schizophrenia as they carry a lower risk of extrapyramidal side effects and tardive dyskinesia than the typical agents.[2,3]

About one-half of individuals with schizophrenia do not, however, respond completely to pharmacotherapy.[2] Refractory schizophrenia is defined as a failure to respond to two trials of antipsychotics.[2] Clozapine, one of the second generation antipsychotics, is considered the treatment of choice in these patients; however, it carries the risk of serious blood dyscrasias, requiring weekly to bi-weekly monitoring of blood counts.[2] Amisulpride, also a second generation agent, may be an alternative to clozapine for managing schizophrenia and is available in Canada through the Special Access Program.[4] There are, however, safety concerns with amisulpride. QT interval prolongation and torsades des pointes cardiac arrhythmias have been reported with its use, which prompted a warning letter from Health Canada in 2004, cautioning that the risk versus benefit of treatment be carefully considered when using amisulpride.[4]

This report will review evidence of clinical effectiveness and safety of amisulpride in the management of schizophrenia that has been published since 2004.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of amisulpride for adult patients with refractory schizophrenia?

2. What is the clinical evidence regarding the safety of amisulpride for adult patients with refractory schizophrenia?

KEY MESSAGE

Results from one non-randomized study suggest that the odds of remission, recovery or adequate quality of life with both amisulpride and clozapine were not statistically different from olanzapine. When just those patients in the study who remained on the same treatment for 36 months were considered, the odds of remission with amisulpride and clozapine was lower than olanzapine.

METHODS

A limited literature search was conducted on key resources including Ovid MEDLINE, EMBASE, PsycINFO, PubMed, The Cochrane Library (2011, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, non-randomized studies containing safety data, and safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and May 6, 2011.

Studies were eligible for inclusion if they evaluated amisulpride and clozapine in the management of schizophrenia and reported on clinical effectiveness or serious adverse events such as cardiac arrhythmias or QT interval prolongation. Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials (RCTs) and non-randomized studies were eligible for inclusion; case reports were excluded.

SUMMARY OF FINDINGS

Two relevant reports from a non-randomized study were identified by the literature search, both of which reported on clinical effectiveness.[5,6] No relevant health technology assessment reports, systematic reviews, meta-analyses, or RCTs were identified. One non-randomized study that reported on QT interval prolongation with amisulpride[7] was identified, but did not include clozapine as a comparator and, thus, did not meet the inclusion criteria for this report.

Non-randomized studies

The characteristics of the included non-randomized studies are summarized in Table 1. Both reports of the Schizophrenia Outpatient Health Outcomes (SOHO) study included 36-month outcomes. The SOHO study was a prospective cohort study that was conducted in 10 countries in Europe, with 1096 psychiatrists enrolling patients. The purpose of the SOHO study was to compare the effectiveness of olanzapine to other second generation antipsychotics in

individuals with schizophrenia. Interventions included amisulpride, clozapine, olanzapine, quetiapine and risperidone. Selection of antipsychotic medication was at the discretion of the psychiatrist. The majority of patients (90.4%) had been previously treated for schizophrenia, but it was not clear if they would meet the criteria for refractory schizophrenia as defined in the Canadian Psychiatric Association guidelines.[2]

The two reports analyzed different subsets of patients enrolled in the SOHO study. Novick et al.[6] reported outcomes for all those patients who had data available at the 36-month follow-up, whereas Haro et al.,[5] based their analysis on only those patients who maintained treatment with the same antipsychotic for the entire study (which they refer to as 'completers').

Table 1: Study characteristics of relevant reports

Study	Methodology	Population	Interventions	Patient Characteristics
Novick et al., 2009*[6]	Prospective, observational study carried out in 10 European countries. 36 month follow-up results.	Patients with schizophrenia aged 18 and older with schizophrenia that were initiating or changing treatment with an antipsychotic medication. Outpatients and inpatients that would be discharged from hospital within two weeks. No restriction on reason for medication change (lack of efficacy, adverse effect, initial treatment)	Amisulpride • n=208 • Mean dose: 456 mg Clozapine • n=272 • Mean dose: 267 mg Olanzapine • n=2501 • Mean dose: 12 mg Risperidone • n=966 • Mean dose: 5 mg Quetiapine • n=292 • Mean dose: 460 mg	Male: 57.6% Average age of cohort at study initiation: 40.2 years (SD=12.9) Years since first treatment: 11.8 (SD=11.0) Previously untreated: 9.6%
Haro et al., 2006*[5]	Prospective, observational study carried out in 10 European countries. 36 month follow-up results.	Patients with schizophrenia aged 18 and older with schizophrenia that were initiating or changing treatment with an antipsychotic medication. Analysis included only those who maintained treatment with the same antipsychotic for the entire study (completers). Outpatients and inpatients that would be discharged from hospital within two weeks. No restriction on reason for medication change (lack of efficacy, adverse effect, initial treatment)	Amisulpride • n=83 • Mean dose: 439 mg Clozapine • n=141 • Mean dose: 257 mg Olanzapine • n=2072 • Mean dose: 12 mg Risperidone • n=694 • Mean dose: 5 mg Quetiapine • n=143 • Mean dose: 440 mg	Male†: 57.6% Average age at first treatment for schizophrenia**: 28.5 years (SD=10.2) Years since first treatment†: 11.8 (SD=11.0) Previously untreated†: 9.6%

SD= standard deviation
* Both studies present results from the Schizophrenia Outpatient Health Outcomes (SOHO) Study; however, for Haro et al., the analysis was based on patients who maintained treatment with the same antipsychotic for the entire study (completers).

† Demographics characteristics were reported for the entire SOHO population, not specifically for the 'completers'** Age at which patients first received any treatment for schizophrenia, which was prior to the SOHO study for most participants.

Study outcomes, authors' conclusions and limitations are summarized in Table 2. Only outcomes of the two drugs of interest, amisulpride and clozapine, are presented. Results were presented for each drug relative to olanzapine. Novick et al.,(2009)[6] found a higher discontinuation rate with amisulpride (54%) compared to clozapine (33%). No statistical analysis was presented for this outcome and the reason for discontinuation was not reported. Novick et al. (2009)[6] found that the odds of achieving symptomatic remission, functional remission, achievement of adequate quality of life or recovery with amisulpride and clozapine was not statistically different from olanzapine (Table 2). In the analysis of completers, Haro et al.,(2006)[5] found that the odds of remission was lower with amisulpride and clozapine compared to olanzapine (Table 2). The likelihood of relapse with amisulpride and clozapine was not statistically different than olanzapine.

Table 2: Study outcomes, conclusions and limitations

Study	Outcomes	Authors' Conclusions	Limitations
Novick et al., 2009[6]	Discontinuation rate†: Amisulpride: 54% Clozapine: 33% Symptomatic remission: Amisulpride OR‡=0.94; p=0.75 Clozapine OR‡=0.94; p=0.75 Functional remission: Amisulpride OR‡= 0.64; p=0.14 Clozapine OR‡=0.56; p=0.09 Adequate quality of life: Amisulpride OR‡= 0.87; p=0.50 Clozapine OR‡=1.10; p=0.61 Recovery*: Amisulpride OR‡= 1.16 (95% CI: 0.51 to 2.67); p=0.73 Clozapine OR‡=0.43 (95% CI: 0.13 to 1.45); p=0.17	A very low proportion of patients achieve recovery and type of antipsychotic medication is one important predictor of recovery.	The proportion of patients who had refractory schizophrenia was not reported. This could limit the generalizability of the results to the population with refractory disease; however, over 90% had been previously treated. The study was not randomized, which could increase the risk of confounding compared to a RCT. The study was not blinded, which could increase the risk of observer bias when assessing the outcomes. Odds ratios for amisulpride compared to clozapine were not reported. Odds ratios for each drug were relative to olanzapine. The dosage of clozapine was, on average, lower than the usual target dose of 300 mg to 600 mg, whereas the olanzapine group was treated on average with a dosage in the target range of 10 mg to 20 mg.[2]
Haro et al., 2006[5]	Remission**: Amisulpride OR‡= 0.73 (95% CI: 0.56 to 0.94); p=0.01 Clozapine OR‡=0.78 (95% CI: 0.65 to 0.95); p=0.01 Relapse:	There were no relevant differences between clozapine and olanzapine in outcomes, but the results should be interpreted conservatively given the observational study design.	The proportion of patients who had refractory schizophrenia was not reported. This could limit the generalizability of the results to the population with refractory disease; however, over 90% had been previously treated. The study was not randomized, which

Study	Outcomes	Authors' Conclusions	Limitations
	Amisulpride HR‡= 1.38 (95% CI: 1.00 to 1.90); p=0.053 Clozapine HR‡=1.09 (95% CI: 0.78 to 1.53); p=0.62		could increase the risk of confounding compared to a RCT. The study was not blinded, which could increase the risk of observer bias when assessing the outcomes. Odds ratios for amisulpride compared to clozapine were not reported. Odds ratios for each drug were relative to olanzapine. The dosage of clozapine was, on average, lower than the usual target dose of 300 mg to 600 mg, whereas the olanzapine group was treated on average with a dosage in the target range of 10 mg to 20 mg.[2]

CI: Confidence interval; HR: Hazard ratio; OR: Odds ratio; RCT: Randomized controlled trial
* Defined as symptomatic and functional remission with an adequate quality of life for a minimum of 24 months, maintained until the 36-month visit.
** Defined as mild severity of symptoms for six months or longer. As well, the individual must not have been hospitalized for schizophrenia during this time.
† No statistical analysis reported
‡ OR's and HR's are compared to the olanzapine group

Limitations

The literature search identified two reports from a non-randomized study in which the clinical effectiveness of amisulpride and clozapine in patients with schizophrenia was reported. No higher quality evidence (health technology assessment reports, systematic reviews, meta-analyses, or RCTs) was identified. No studies with safety data were identified that met the inclusion criteria for this rapid review. Thus, the evidence of the comparative safety and effectiveness of amisulpride and clozapine is sparse.

The included reports had a number of limitations, related to the non-randomized design, which could increase the risk of bias and confounding. Moreover, the generalizability of the included studies is unclear given that the dose of clozapine appeared to be lower than what is recommended as the target in Canadian guidelines.[2] Generalizability to those with refractory schizophrenia could also be compromised by the inclusion of approximately 10% of participants who did not meet the definition of refractory disease since they had not been previously treated. In addition, the interpretation of the study outcomes was complicated by the manner in which they were presented in the study. Comparisons were made between each drug and olanzapine, rather than directly to each other.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The evidence published since 2004 comparing the clinical effectiveness and safety of amisulpride and clozapine is sparse, limited to two reports from one non-randomized study. Results of this study suggest that there are no statistical differences in the clinical effectiveness of either drug, relative to olanzapine, for recovery, relapse, and quality of life; however, caution is recommended in interpreting the results of this study, given its limitations. The comparative

safety (serious adverse effects) for amisulpride and clozapine could not be determined from the identified literature, so no conclusions can be made for this outcome.

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