

FOR YOUR INPHARMATION



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Amisulpride (Solian®)

INTRODUCTION

Amisulpride is a substituted benzamide antipsychotic structurally related to sulpiride. (For a review of sulpiride, please refer to Riverview Hospital's For Your InPharmation Newsletter Volume #21, Issue #18 – December, 2001) Amisulpride is indicated for the treatment of acute and chronic schizophrenia with prominent positive and/or negative symptoms. Its effectiveness in the improvement of both the positive and negative symptoms is related to a dose-dependent blockade of dopamine receptors. In addition to antipsychotic effects, preliminary reports suggest that amisulpride may have antidepressant effects in dysthymia.

Pharmacology (see Table 1)

Amisulpride has high affinity for the dopamine D₂/D₃ receptors and has little or no affinity for D₁, D₄, D₅, serotonin, α -adrenergic, H₁ histaminergic or anticholinergic receptors. Amisulpride has limbic selectivity, which is associated with a low propensity for causing extrapyramidal side effects (EPSE). This drug represents a rational alternative for schizophrenic patients where sedation, weight gain or antimuscarinic effects are contraindicated or have been problematic previously.¹

At low doses (100mg/day), amisulpride enhances dopamine transmission by selectively binding to presynaptic autoreceptors, contributing to its efficacy in primarily negative symptoms.

At high doses (400-800mg/day), amisulpride inhibits dopamine transmission by blocking postsynaptic D₂/D₃ receptors in the limbic system, which is predicative of potent antipsychotic activity (positive and negative symptoms).

Pharmacokinetics

Bioavailability is approximately 36% when given orally. The volume of distribution is 9 -16 L/Kg. Plasma protein binding is 17%. Amisulpride has two absorption peaks, one hour and three to four hours post-dose. The elimination half-life is 12 hours. Metabolism is limited with most of the drug excreted unchanged in the feces (64%) and in the urine (33%). There are two inactive metabolites with the principal metabolite (N-oxide) accounting for 4-10% of the total load excreted.

Clinical Studies (see Table 2)

Schizophrenia studies

- A 2002 Cochrane Review³ evaluated the effects of amisulpride comparing it with placebo, typical, and atypical antipsychotic drugs for schizophrenia. This review consists of 19 randomized studies with a total of 2443 participants. Most trials were of short duration.

Four trials with 514 participants with predominantly negative symptoms suggested that a low dose (up to 300mg/day) of amisulpride was a more acceptable treatment than placebo, evidenced by improvement in the global state score and treatment of negative symptoms.

A total of 14 trials compared amisulpride to typical antipsychotic agents. The pooled results suggest amisulpride was superior in improving global state, general mental state and negative symptoms of schizophrenia and as effective as typical antipsychotics with regard to positive symptoms.

One multi-center, multi-national, randomized double blind trial^{3,9} (n=228) compared amisulpride (AMS) (800mg/day, n=115) to risperidone (8mg/day, n=113)

for 8 weeks. Both treatments were equally effective for positive symptoms (PANSS+), however, AMS had a greater improvement in negative symptoms (PANSS-). Both drugs showed good safety profiles with respect to objective measurements on tardive dyskinesia (AIMS) and akathisia (BAS). Patients in the risperidone group experienced a significantly greater increase in weight than the AMS group, while patients in the AMS group experienced more frequent agitation. However, an 8mg/day dose of risperidone does not accurately reflect current clinical practice for most patients.

The results of the Cochrane Review suggest that amisulpride is an effective antipsychotic for schizophrenia. It may yield better efficacy results in the global state and general negative symptoms and may be more acceptable and tolerable than high-potency typical antipsychotics especially regarding EPSE. Longer term randomized trials are needed to evaluate its effects particularly compared to the atypical antipsychotics.

- Another multi-center, double blind, randomized study⁵ (n=309) evaluated the efficacy, safety and functional effects of amisulpride (400-1000mg/day) and risperidone (4-10mg/day). There was no difference on the symptomatic improvement between the two groups, but amisulpride was significantly superior to risperidone in subjective response and functional effects (PANSS, BPRS, and CGI). Both treatments were well tolerated and demonstrated similar low incidence of EPSEs, however, amisulpride was associated with less weight gain and endocrine/sexual symptoms.

Dysthymia Studies (see Table 3)

Preliminary studies in patients with dysthymia (Smerald¹¹ 1998, Lecrubier et al¹² 1997, Boyer et al¹³ 1999) that compared amisulpride with fluoxetine, imipramine, and amineptine with placebo support the clinical observation that amisulpride may have antidepressant activity¹⁰. More clinical studies are needed to substantiate this observation.

Common Adverse Effects

At low doses (up to 300mg/day) the incidence of adverse effects was similar to placebo. At higher doses (>300mg/day) it has adverse effects such as adverse endocrinologic effects, agitation, insomnia and anxiety at about the same rate as other

antipsychotics. It has a dose-dependent EPSE. At higher doses, amisulpride has less EPSE than haloperidol or flupenthixol^{6,8,17} and more weight gain than haloperidol, but less weight gain than risperidone and olanzapine.^{6,9,20}

- *Cardiovascular*: Rare reports of hypotension at high doses¹⁴, bradycardia, isolated cases of QT prolongation¹⁵.
- *CNS*: Somnolence or drowsiness (2%), insomnia, agitation, anxiety (5-10%)
- *EPSE*: Acute dystonia¹⁴, tardive dyskinesia (TD)¹⁴, EPSE (tremor, stiffness)
- *Endocrine/Metabolic*: Hyperprolactinemia, galactorrhoea, gynaecomastia, amenorrhoea, breast pain or irregular periods, libido disturbance¹⁴, weight gain¹⁴.
- *Gastrointestinal*: Nausea, vomiting, constipation, and dry mouth (2%).
- *Hepatic*: No hepatitis reported.⁴
- *Hematological*: No agranulocytosis reported.⁴
- *Neurological*: Rare cases of NMS, seizure threshold reduction.
- *Skin*: No serious cutaneous or allergic adverse reaction reported.

Recommended Monitoring

The manufacturers give no recommendation for monitoring criteria before or during treatment. However, patients should be counseled to report any signs and symptoms of endocrine, EPSE or other bothersome adverse effects.

Cautions

Contraindicated: hyperthyroidism, prolactin-dependent tumor, pheochromocytoma, hypersensitivity to amisulpride, other benzamide derivatives and nonmedicinal ingredients, children up to puberty, breast-feeding. The use of amisulpride is not recommended during pregnancy.

Special Warnings and Special Precautions:

Patients suffering from severe renal failure, epilepsy or Parkinson's disease should be closely monitored. Reduced renal function may require dosage adjustments. Elderly patients may have increased sensitivity to hypotension and sedation.

Drug Interactions (not all-inclusive)

Amisulpride may-

- enhance the central effect of alcohol
- antagonize the effect of levodopa, carbamazepine, phenytoin, valproate, sympathomimetics
- potentiate the hypotensive effect of antihypertensives
- enhance the CNS effects of hypnotics, tranquilizers, anaesthetics, antihistamines, morphine derivatives, barbiturates, benzodiazepines
- increase the plasma concentrations of tricyclic antidepressants and ritonavir
- increase the risk of ventricular arrhythmia with drugs which prolong QT interval
- increase the risk of extrapyramidal effects of tetrabenazine

Avoid concomitant use of amisulpride with ropinirole and sibutramine as recommended by the respective manufacturers.²¹

Dosing Information

No specific titration is required when initiating treatment.

Adult Dosage:

- Acute psychotic episode in schizophrenia: 400-800mg /day in divided doses (BID). Doses above 400mg should be administered twice daily. Maximum recommended daily dose is 1200mg.
- Patients with predominantly negative symptoms who are not acutely psychotic: 50-300mg/day, the optimal dose is 100mg/day.⁷

(PANSS+/-)=Positive and Negative Symptom Scale positive/negative syndrome sub-scale; AIMS=Abnormal Involuntary Movement Scale; SAS=Simpson Angus Scale; BAS=Barnes Akathisia Scale; BPRS=Brief Psychiatric Rating Scale

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Dosage adjustment in renal failure: The dose should be halved if the CrCl is 30-60 mL/min. and reduced to one-third for CrCl between 10-30 mL/min.¹⁵

Amisulpride is not recommended for children.

Summary

Amisulpride is an antipsychotic structurally similar to sulpiride. Its selectivity for the D₂/D₃ receptors and low or no affinity for other receptors offers a very low incidence of cardiotoxicity, hypotension, sedation and anticholinergic symptoms. Its favorable characteristics also include low incidence of EPSE and weight gain. However, it has a high incidence of prolactin elevation.

Clinical studies have supported that amisulpride (400-1200mg/day) is at least as effective as haloperidol and risperidone and more effective than flupenthixol in acute exacerbation. Its efficacy during long term treatment exceeded haloperidol. In the treatment of patients with predominantly negative symptoms, amisulpride was more effective than placebo, but no more effective than haloperidol or fluphenazine. No comparison studies with atypical antipsychotics other than risperidone have been published to date.

Availability

Oral amisulpride is available in Canada as a patient specific medication through the Special Access Program (Once approved, it may be purchased from the manufacturer). It is marketed in several European countries (United Kingdom in 1997), Australia under the name Solian[®] (Lorex-Synthelabo) and in the Philippines (Sanofi-Synthelabo). It is not available in the United States, but a program of clinical development is ongoing.

Table 1 - Receptor Binding Profiles of Amisulpride, Haloperidol, Clozapine, Olanzapine, Risperidone, Quetiapine, Ziprasidone

Receptor	Amisulpride	Haloperidol	Clozapine	Olanzapine	Risperidone	Quetiapine	Ziprasidone
D ₁	-	+++	+++	+++	+++	+	+++
D ₅	-	+	+	NA	NA	NA	NA
D ₂	+++ /++++	+++++	++	+++	+++++	++	++++
D ₃	++++	++++	++	++++	++	++	++++
D ₄	-	+++++	++++	++++	+++++	-	+++
5HT _{1A}	-	+	++	+	++	++	++++
5HT _{2A}	-	+++	++++	++++	+++++	++	+++++
Alpha-1	-	+++	+++	+++	++++	++++	+++
Alpha-2	-	+	+++	++	++++	+++	+-
H ₁	-	+	++++	++++	+++	++++	+++
M ₁	-	+	+++ /++++	++++	+-	+++	-

NA = Not available

Adapted from P.Seeman, 1993; Bezchlibnyk-Butler et al, 2001

K₁ (nM) >100,000 = “-”; 10,000-100,000 = “+-”; 1000-10,000 = “+”; 100-1000 = “++”; 10-100 = “+++”; 1-10 = “++++”; 0.1-1 = “+++++”

Table 2 - Therapeutic Efficacy of Amisulpride¹⁶

Comparison with / dosage	Number of /Type of Study	Duration	Result
<i>Acute exacerbations of schizophrenia</i>			
Amisulpride(AMS) / haloperidol 400-1200mg/d / 5-40mg/day	5 Randomized, double blind	3 -6 weeks	Similar positive symptoms improvement. One study showed significant more improvement with AMS in negative symptoms. 3 studies showed AMS was better in improving affective symptoms with superior results after 1-2 weeks.
AMS / Flupenthixol 1000mg/day 25mg/day Wetzel et al, 1998	1 Randomized, double blind, parallel, n=133	6 weeks	AMS showed greater improvement in the positive and negative symptoms, also improvement in symptoms of retardation and depressed mood noted using Bech-Rafaelsen melancholic scale(BRMS)
AMS / Risperidone 800mg/day 8 mg/day	1 Randomized, double blind, n=228	8 weeks	Similar improvement in general symptomatology, social functioning, and coping ability. Also, sub-score analysis showed in favor of AMS in negative symptom improvement
<i>Chronic Schizophrenia</i>			
AMS / Haloperidol 400-1200mg/day 10-30mg/day	2 long term comparative trials with flexible dosages	16 weeks, 52 weeks	AMS was found to have rapid improvement in both positive and negative sub-scores and maintained for duration of the trials. PANSS negative sub-scores were statistically superior with AMS in both trials. PANSS positive sub-scores were similar in both trials. Improvement in BPRS total score was significantly greater with AMS in the 52 wk. Trial.
AMS / Risperidone 600mg/day 6mg/day then adjustable then adjustable 400-1000mg/day 4-10mg/day	1 Randomized, double blind ²	6 months	Similar improvement in social functioning (SOFA), mean BPRS total score and Total PANSS score with favorable trend with AMS in PANSS negative sub-score and CGI
<i>Predominantly negative symptoms</i>			
AMS / Placebo	4 Randomized, double blind, placebo, controlled ⁴		AMS ≤300mg/day was more effective than placebo
AMS / Haloperidol 100-800mg/d → 3-20mg/day→ 100-150mg/d 3-4.5mg/day	1 Randomized, double blind	1 year	Over one year period, AMS is as effective as haloperidol in preventing relapse
AMS / Fluphenazine or haloperidol	3 Randomized		AMS has similar effects

Table 3 - Therapeutic Efficacy of Amisulpride in Dysthymia or Major Depression

Comparison with / dosage	Type of Study	Duration	Result
Amisulpride(AMS) / Fluoxetine 50mg/day 20mg/day (Smeraldi E. 1998) ¹¹	Multi-center, randomized, double-blind, parallel (n=281)	3 months	The baseline Montgomery and Asberg Depression Rating Scale (MADRS) total score was reduced by at least 50% in 74.1% (103/139) of the AMS patients and 67.4% (87/129) of the fluoxetine patients. There were no significant differences in the reductions in the mean total score with the MADRS, Widlocher Psychomotor Retardation Scale, Sheehan Disability Scale and CGI between the 2 groups. AMS (63%) decreased anxiety significantly more than fluoxetine (54%), measured by the mean total score of HAM-A. There were 13 dropouts with AMS due to adverse events and 10 with fluoxetine. The most common adverse events were endocrine-like events in female patients with the AMS group and gastrointestinal adverse events with the fluoxetine group.
AMS / Imipramine 50mg/day 100mg/day (Lecrubier, Y. et al 1997) ¹²	Multi-center , placebo-controlled (n=219)	6 months	Both Intention-to Treat and Per Protocol analysis showed significant differences between the groups (active treatment vs placebo) on all main rating scales (CGI, MADRS, ERD, SANS). The imipramine group reported higher adverse event than the other 2 groups mainly due to its anticholinergic effects. Endocrine-like effects were more frequent in female patients in the AMS group.
AMS / Amineptine 50mg/day 200mg/day (Boyer, P. et al 1999) ¹³	Multi-center, Placebo-controlled (n=323)	3 months	AMS (63%) and amineptine (64%) were found to be statistically superior to placebo (33%) in the treatment of primary dysthymia (CGI) respectively, improvement in MADRS and SANS scores were twice as high as placebo with AMS and amineptine treatment. The adverse event profile of AMS was similar to placebo except for endocrine effects in female patients. The main adverse event profile of amineptine showed psychic activation (insomnia, nervousness). The results show that AMS can improve symptoms of chronic depression in dysthymia.

CGI=Clinical Global Impression; ERD=Widlocher Depressive Retardation Scale; SANS=Scale for the Assessment of Negative Symptoms

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