Psychiatr. Pol. ONLINE FIRST Nr 142: 1–13
Published ahead of print 29 July 2019
www.psychiatriapolska.pl
ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
DOI: https://doi.org/10.12740/PP/OnlineFirst/109129

Amisulpride – is it as all other medicines or is it different? An update

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Summary

Amisulpride is an antipsychotic available in Europe since 1990s, in Poland since 2000. Subsequent years brought to Polish market more second-generation compounds such as ziprasidone and aripiprazole. In 2018, the Agency for Health Technology Assessment and Tariff System issued positive recommendation for lurasidone in schizophrenia (Recommendation 30/2018) facilitating its entry to the market. Thanks to new molecules, therapeutic possibilities of medicines consequently rise, however, higher number of available substances of different properties brings also more dilemmas which one to pick. Since new publications of comparative drug trials, meta-analyses and systematic reviews are issued regularly, the authors present herein publications issued within last ten years focusing on amisulpride as opposed to other neuroleptics used in Poland. Although in many aspects it is equivalent to other atypical antipsychotics, it still has some advantages. Amisulpride seems to have better outcome than classic and atypical neuroleptics when it comes to depressive symptoms and predominant negative symptoms. It might also be superior to haloperidol in inducing symptomatic remission in first episode schizophrenia. Except for prolactin increase its side effects profile is favorable – it rarely leads to extrapyramidal symptoms (which are dose-dependent) and sedation. Therefore many patients accept treatment with amisulpride for its measurable clinical gains, such as improvement of positive symptoms and higher quality of life, compared to typical neuroleptics. Pharmacokinetics of amisulpride also encourage its wider use, especially when there is either a need for combined psychopharmacotherapy or comorbidity with general medical condition rises a need for somatic parallel treatment.

Key words: psychosis, amisulpride, clinical effectiveness

Introduction

Since 1952, the year when chlorpromazine was first introduced to the market, the era of psychopharmacotherapy is in its ascendance. It transformed contemporary psychiatry of social exclusion of the insane into modern psychiatry of their reintegration with the society. It is the very virtue of the subsequent more and more efficient and selective antipsychotics. Modern psychiatry has at its disposal a wide gamut of compounds of proven effectiveness. Today, leaning on our personal clinical experiences and even more on evidence-based medicine (EBM), we can chose from many medicines prescribing these to our patients in an individualized manner supporting them in overcoming psychotic crisis. By selecting the right substance we attempt to maximize the therapeutic effect that is not only to alleviate the symptoms of the disorder but also to minimize the undesired side effects of the treatment. The ultimate goal is the resumption of once lost social roles leading to improved quality of life of the patient and their close relatives bearing the burden of mental illness in the family [1].

Well-adjusted treatment should be effective for and acceptable by the patient. Lack of compliance in treatment, a derivative of impaired insight and disagreement to adverse effects might ruin even the best, at least according to EBM, medicine. Amisulpride with some of its properties seems to stand out amidst antipsychotic drugs. According to EBM, it seems to be equally effective against positive symptoms as haloperidol, yet without its extrapyramidal adverse effects [2]. It might be one of the few neuroleptics efficient in treatment of predominant negative symptoms [3]. It is also safe in combination with many other psychiatric and general medicines [4]. It rarely leads to sedation [5] and its weight gain effect seems to be moderate [5, 6]. An important flaw of amisulpride and potential obstacle for some patients might be its prolactin increase effect [5, 6].

This article aims at reviewing publications from last decade of original first – and second-generation antipsychotic drug comparative studies and meta-analyses from the perspective of amisulpride with special consideration for its clinical efficacy and adverse effects profile in comparison to other drugs. Despite the fact that amisulpride has not got a registration in old age patients, its use in this very group was also taken into review.

The history

The group of second-generation antipsychotics encompasses several classes of neuroleptics one of which are benzamides. First derivative of the substituted benzamide was sulpiride synthesized in 1964 [7]. In subsequent years, other derivatives such as sultopride, tiapride and metoclopramide were produced [8]. Last was amisulpride synthesized in 1975 [7]. It took another fifteen years before it was made available to patients in France in 1990 and ten more for it to enter the Polish market in 2000 [4]. Not all benzamide derivatives proved effective and safe in clinical practice. Remoxipride introduced to the market in the 1990s had to be withdrawn as soon as it was demonstrated that the drug was responsible for lethal instances of aplastic anemia occurring with the frequency of 1:10,000 [8]. In Poland, the following compounds are in use:

sulpiride and amisulpride; metoclopramide – an antiemetic agent, and tiapride – the only one in the group officially registered for patients in advanced age with dementia and disrupted behaviors.

The pharmacology

Because of its pharmacodynamic properties, amisulpride is a unique antipsychotic. It has no affinity to the dopamine D_1, D_4 and D_5 receptors and no affinity (or only minor) to serotoninergic, noradrenergic, histaminergic, and cholinergic receptors [9]. This might explain its beneficial profile of adverse effects and clinical safety in patients with concomitant somatic disorders [6]. Amisulpride displays selective affinity to D_2 and D_3 receptors and this effect is dose-dependent. In low doses, i.e., ≤10 mg/kg of body weight, it is a dopamine agonist reacting with presynaptic receptors stimulating dopamine excretion to the synaptic cleft. With higher doses amisulpride binds to post-synaptic receptors exerting blockade and having antagonistic effect on dopaminergic system, which is responsible for antipsychotic action of the drug [7].

Additionally, amisulpride has systemic selectivity since it binds preferentially to dopamine receptors in mesolimbic regions rather than to receptors in the striatum. That is why it causes less extrapyramidal symptoms than other neuroleptics and improves affective and cognitive functioning [7]. Moreover, its receptor binding time is short when opposed to risperidone (42 seconds vs. 28 minutes) [10], which might translate into low risk of tardive dyskinesias [7]. Pharmacokinetic properties also distinguish amisulpride from other drugs. Studies on healthy volunteers taking single dose of 50 mg revealed two peaks of absorption – an hour after the drug intake and four hours later. The total bioavailability reaches 50%, distribution volume is approximately 5.8 kg/l and plasma protein binding averages 17% [9]. The latter parameter is highly in favor of amisulpride and its clinical safety when the drug is combined with other medicines – the risk of these being displaced from plasma protein binding sites is low [11]. Similarly, the fact that only small proportion of amisulpride is metabolized in the liver and the majority of the drug is excreted unchanged by kidneys, makes it safe choice for combined treatment [12]. The risk of reciprocal interactions between drugs on the cytochrome P450 level is also low [13].

Renal clearance of amisulpride in healthy subjects reaches approximately 20 l/h and might decrease with age; it decreases significantly in the case of renal failure [7]. There is a linear relationship between the daily dose and plasma concentration of amisulpride. With the dose of 400–800 mg the D_2 receptor saturation level is optimal as well as is the clinical response. This oral dosage corresponds to the plasma concentration of 100–320 ng/ml. The concentration below 100 ng/ml is considered to be under the threshold for clinical response, whereas concentration above 320 ng/ml brings the risk of extrapyramidal symptoms [14].

In the case of old age patients, including patients with dementia in Alzheimer's disease, who receive neuroleptics due to positive symptoms, agitation or aggression, therapeutic window of amisulpride is different than the one mentioned above for the young patients. In patients >65 years of age, amisulpride dosage of 25–75 mg daily

brings antipsychotic effect, and the minimal plasma concentration level needed to achieve this effect is 20 ng/ml, which corresponds to D_2/D_3 receptors occupancy of 43% (caudate nucleus), 25% (putamen) and 43% (thalamus). Extrapyramidal side effects occur with the concentration over 60 ng/ml and D_2/D_3 receptors occupancy of 61% (caudate nucleus), 49% (putamen) and 69% (thalamus) [15].

Formal and legal guidelines for reimbursement and treatment

Summary of Product Characteristics (SPCh) constitutes the reference in the process of clinical decision making and reimbursement. The only legal indication in Poland for amisulpride is: "treatment of acute and chronic schizophrenic disorders in which positive symptoms (such as delusions, hallucinations, thought disorder) and (or) negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterized by predominant negative symptoms" [16]. It is also the only indication for the National Insurer to reimburse the treatment with amisulpride. For acute psychotic episodes with predominant positive symptoms oral doses between 400 and 800 mg daily are recommended. Doses above 1,200 mg have not been evaluated for safety and therefore are not recommended. For patients with predominant negative symptoms SPCh recommends doses between 50 and 300 mg.

Amisulpride in first-episode schizophrenia and schizophreniform disorder – EUFEST and OPTiMiSE studies

Results of the European First-Episode Schizophrenia Trial (EUFEST), which recruited 498 patients, were published in 2009 [17]. It was an open randomized clinical trial conducted in Israel and 13 European countries, including Poland. Eligible patients were 18–40 years of age (mean age 26 years) and met DSM-IV criteria for schizophrenia (53%), schizophreniform (40%), or schizoaffective disorder (7%). All patients have had the first episode of psychosis, which meant that no more than 2 years had passed since the onset of positive symptoms and no antipsychotic had been used exceeding 2 weeks in the previous year or 6 weeks lifetime. Patients were followed up for 12 months and two dichotomized variables based on PANSS [18] scores were considered as a measure of clinical effectiveness. The first was the response rate of ≥50% reduction in the PANSS total score ((PANSSbaseline − PANSSfollow-up) × 100/PANSSbaseline); and the second was remission defined according to Andreasen criteria [19] as a score of ≤3 points ('mild' severity of symptom or less) on eight predefined PANSS items (i.e., delusions, conceptual disorganization, hallucinatory behavior, blunted affect, social withdrawal, lack of spontaneity, mannerisms/posturing, and unusual thought content), each maintained for at least 6 months.

Patients were randomly and without blinding assigned to haloperidol (1–4 mg/d), amisulpride (200–800 mg/d), olanzapine (5–20 mg/d), quetiapine (200–750 mg/d), or ziprasidone (40–160 mg/d) group. Study proved that ≥50% response rate was the highest in the amisulpride and olanzapine group: 67% of the patients in each group had improved clinically; the result was the worst for haloperidol (37%) and the dis-

crepancy was statistically significant (Hazard Ratio (HR) amisulpride vs. haloperidol 2.27, 95% Confidence Interval (95% CI) 1.51 to 3.42, $p = 0.001$). Ziprasidone and quetiapine were in-between haloperidol and amisulpride and the result of haloperidol was statistically similar to quetiapine. Within 12 months remission was seen most frequently in the olanzapine (41%) and amisulpride group (40%), whereas haloperidol was least effective (17%). The difference was statistically significant (HR amisulpride vs. haloperidol 2.49, 95%CI 1.43 to 4.35, $p = 0.012$).

Second-generation neuroleptics did not differ with respect to both variables of clinical effectiveness assumed for the purpose of the trial. In 12th month of follow-up, still more patients on amisulpride or olanzapine displayed symptomatic remission, i. e., approximately 37–38% when opposed to the group treated with haloperidol (17%). Moreover, the authors of the study ascertained that amisulpride proved to be the strongest predictor of ≥50% response rate or remission within 12 months of treatment of the first episode of psychosis, especially when compared to haloperidol. However, limitations of the EUFEST study have to be taken into consideration as these might have biased the results. The dose of haloperidol was low, blinding procedure was lacking so clinicians' preferences for the medicines could have influenced their judgment, intervals between PANSS assessment points were too long and in the case of missing data because of, for instance, lost to follow-up, a technique of last observation carried forward was used.

Another study providing newer evidence on amisulpride potential is the more recent OPTiMiSE trial (The Optimization of Treatment and Management of Schizophrenia in Europe), which was published in 2018 [20]. In favor of amisulpride is its clinical effectiveness similar to olanzapine yet with less adverse effects, especially in long term perspective. The OPTiMiSE study was conducted in Israel and 14 European countries, including Poland. It had three phases: phase 1 of an open-label design which lasted 4 weeks and patients received 200–800 mg/day of amisulpride orally; phase 2 of double-blind randomized design assigning patients to either continue amisulpride (200–800 mg) or switch to olanzapine (5–20 mg/day) during a 6-week period; and finally open-label phase 3 of 12 weeks of treatment with clozapine (100–900 mg). The recruitment criteria and the definition of the first episode of psychosis were identical as those in the EUFEST study. Patients with the first episode of illness (mean age of 26 years; Standard Deviation (*SD*) 6.0) who met DSM-IV criteria for schizophrenia (51%), schizophreniform (43%) or schizoaffective disorder (6%) were recruited. Involuntary patients were excluded. Patients who at the end of phase one or two did not meet modified Andreasen symptomatic remission criteria (i.e., without the time-frame requirement of at least 6 months of the presence of ≤3 points on selected PANSS items) were considered eligible to proceed to the next study phase.

446 individuals entered phase one. 56% of them (250 subjects) achieved remission on amisulpride which was administered in mean dose of 490.4 mg (*SD* 207.4). If all drop-out cases for whatever reason would be skipped in analyses in that phase (75 cases), then the proportion of remissions would rise to 67%. The reasons for drop-out at this stage were as follows: withdrawn consent (28 individuals), adverse events (16), protocol noncompliant (9), lost to follow-up (8), physician's decision (7). Moreover, there were 2 suicide attempts and 5 involuntary hospitalizations.

121 patients not meeting remission criteria were eligible for randomization for switch to olanzapine in phase two but 28 individuals did not proceed further because 22 persons withdrew consent, 4 experienced adverse events, one worsened clinically and one was withdrawn by the physician. After 6 weeks, 34% of phase two patients had remission (32 patients out of 72 who completed phase two). 21 subjects did not complete this phase due to adverse events (7), lack of effectiveness (2), protocol non-compliance (4), 'other reasons' (6), and lost to follow-up (2). In phase two, amisulpride (mean dose 590.9 mg; *SD* 236.1) was equally effective as olanzapine (15.6 mg; *SD* 6.5) in terms of the proportion of remissions on both substances (Odds Ratio (OR) for amisulpride 1.07, 95%CI 0.38 to 2.96) but also in terms of equal reduction of PANSS scores (Standardized Mean Difference (SMD) for amisulpride –3.24, 95%CI – 10.07 to 3.60; $p = 0.35$). Moreover, the number of drop-outs in both therapeutic groups was statistically similar (30% for amisulpride vs. 15% for olanzapine, 95%CI – 2.5 to 30.7; $p = 0.093$). But still, olanzapine was responsible for significant weight gain (4.4 kg; *SD* 3.65 vs. 2.29 kg; *SD* 3.07 for amisulpride; $p = 0.021$). No differences with respect to other side effects (extrapyramidal, sexual disorders) were found between compounds.

Based on these results authors concluded that in the case of first psychotic episode 4-week treatment failure with one neuroleptic (amisulpride) the switchover to another (olanzapine) in subsequent weeks might not be an optimal solution. The OPTiMiSE study showed that patients who continued on amisulpride for the following weeks still had chance to remit or improve clinically to the same extent as those who switched to olanzapine yet without its side effects. The cumulative percentage of remissions on amisulpride after 10 weeks of treatment, i.e., after the second phase, without all drop-outs for whatever reason, was as high as 76%.

28 patients entered the third phase and out of these ten dropped-out in its course (due to, among others, adverse events – 4 cases, withdrawn consent – 2, lost to follow-up – 2). 18 patients completed this phase and 5 (18%) gained remission taking clozapine (mean dose of 279 mg; *SD* 130.2). Additionally, a proportion of patients achieved statistically significant symptomatic improvement on PANSS scores at tenth week of clozapine treatment.

Because in this study the switchover to another antipsychotic after the first one being unsuccessful did not bring higher efficacy than staying on the first medicine for extended period of time, the authors made the suggestion that requirement for clozapine to be used no sooner than after two unsuccessful antipsychotic therapies needs revision. According to their opinion, more rapid introduction of clozapine, without second attempt of treatment with another antipsychotic might shorten time to clinical improvement or remission.

Amisulpride vs. classic and second-generation neuroleptics

The meta-analysis by Leucht et al. [2] published in *Lancet* in 2009, comparing second – and first-generation neuroleptics, was based on 239 publications of 150 studies comprising 21,533 patients with the diagnosis of psychosis (schizophrenia, schizoaffective, schizophreniform or delusional disorder). Only studies of double-blind design

were selected because open or single-blind studies consequently appeared to favor second-generation antipsychotics. The latter ones were represented by amisulpride (50–800 mg), aripiprazole (10–30 mg), olanzapine (10–20 mg), quetiapine (>250 mg), risperidone (4–6 mg), sertindole (16–24 mg), and ziprasidone (120–160 mg). As the first-generation active comparator either haloperidol (95 studies) in the cut-off dose of 7.5 mg and 12 mg daily, or other classic neuroleptic with low antipsychotic potency in chlorpromazine equivalent dose of 600 mg was used (e.g., chlorpromazine, perphenazine, fluphenazine, flupentixol, perazine). Mean age of the patients was 36.2 years, mean duration of the disorder was 11.8 years. Majority of the studies had up to 12 weeks of follow-up, the remainder up to 6 months or longer.

Amisulpride (to similar extent as clozapine, olanzapine and risperidone) proved to be superior to classic neuroleptics in alleviating positive and negative symptoms. Other second-generation neuroleptics (aripiprazole, quetiapine, sertindole, ziprasidone) were comparable to classic ones in their effectiveness against both types of psychotic symptoms. The aforementioned fact suggests that not all new antipsychotic preparations should automatically be seen as better than classic neuroleptics for negative symptoms. Additionally, amisulpride (but clozapine, olanzapine and aripiprazole as well) was characterized by higher efficacy for depressive symptoms than classic neuroleptics. However, in this meta-analysis, it did not show any benefits in relapse prevention when compared to haloperidol. In 14 long-term studies olanzapine and risperidone proved superior to amisulpride in that specific respect. Yet amisulpride had more statistically significant positive impact on quality of life than classic antipsychotics. Out of second-generation neuroleptics only clozapine and sertindole also had similar effect.

The analysis of the adverse effects has shown that all investigated atypical neuroleptics caused definitely less extrapyramidal symptoms than haloperidol even when it was dosed as low as 3–4 mg daily but still were comparable to classic neuroleptics of low antipsychotic potency. Except for aripiprazole and ziprasidone, all other atypical antipsychotics caused weight gain statistically more often than haloperidol but no more than classic low potency neuroleptics. Amisulpride had impact on body weight and the extent of this effect positioned it close to aripiprazole, at least in short-term observation – majority of the studies followed up 12 weeks of treatment.

Another meta-analysis by Leucht et al. [21], published in 2013, involved 13 atypical neuroleptics which were compared to haloperidol, chlorpromazine and placebo. And these were, e.g.: amisulpride, clozapine, olanzapine, ziprasidone, aripiprazole, asenapine, paliperidone, risperidone, sertindole, and quetiapine. The meta-analysis used multidirectional comparisons of two or more drugs with a common comparator. Literature search of material published between 1955 and 2012 returned 212 eligible studies, covering a large group of 43,049 patients. Mean age was 38.4 years (*SD* 6.9) and the mean duration of the disorder was 12.4 years (*SD* 6.6). 99% of studies were double-blind. More than half of these studies, i.e. 144, were carried out for pharmaceutical companies. Individuals with schizophrenia or related disorders (schizoaffective, schizophreniform or delusional disorder) were eligible for this meta-analysis. Patients with predominant negative symptoms, concomitant medical illness, treatment resistance and in stable phase of the illness were excluded. Due to the latter, results cannot

be generalized to such groups of patients. Drugs were prescribed in monotherapy either flexibly individually for each patient or in fix doses up to the maximum doses as indicated by international consensus studies of antipsychotic dosing. The dependent variables were: the mean overall change in symptoms (as measured by the PANSS or BPRS [22]), all-cause treatment discontinuation, weight gain, hyperprolactinemia, use of antiparkinsonian agents as a measure of extrapyramidal side-effects, QTc prolongation, and sedation. Only acute 6-week treatment was considered and it was ensured that the meta-analysis did not make 'unfair' comparisons, i.e., high doses of one drug with small doses of the other.

Haloperidol was administered to patients in dose intervals of less than 7.5 mg to more than 12 mg per day; chlorpromazine doses were of less than 500 mg per day to more than 600 mg per day. All investigated drugs were more efficient than placebo in inducing mean overall change in symptoms but clozapine was the most effective (*SMD* – 0.88, 95% Credible Interval (95%CrI) – 1.03 to – 0.73). Next to it was amisulpride (*SMD* – 0.66, 95%CrI – 0.78 to – 0.53), but also olanzapine and risperidone. Other drugs were less effective. All-cause discontinuation was the measure of the acceptance for treatment and amisulpride had an advantage over other medicines in that very respect. In terms of acceptance for treatment, it was closest to placebo (Odds Ratio (OR) 0.43, 95%CrI 0.32 to 0.57), like olanzapine (OR 0.46, 95%CrI 0.41 to 0.52) and clozapine (OR 0.46, 95%CrI 0.32 to 0.65). It means that drugs from the top of the clinical effectiveness rank (clozapine, amisulpride and olanzapine) are also characterized by highest acceptance for treatment and this might be more due to their clinical efficacy than side effects profiles because about 40% of discontinued treatments in the analyzed studies resulted from lack of clinical improvement and only 17% form adverse effects.

In terms of weight gain effect, olanzapine was the worst (*SMD* 0.74, 95%CrI 0.67 to 0.81) and haloperidol was the best drug (*SMD* 0.09, 95%CrI – 0.00 to 0.17). Amisulpride (*SMD* 0.20, 95%CrI 0.05 to 0.35) ranked just behind ziprasidone and aripiprazole but ahead of paliperidone and risperidone. In comparison to placebo clozapine caused less extrapyramidal symptoms, whereas amisulpride was similar to placebo (OR 1.6, 95%CrI 0.88 to 2.65). Due to insufficient data, the meta-analysis did not provide any information on prolactin release during amisulpride treatment. Against previous ascertainments, amisulpride showed significant QTc prolongation effect (OR 0.66, 95%CrI 0.39 to 0.91) and ranked closely to sertindole (OR 0.90, 95%CrI 0.76 to 1.02). It has to be mentioned that this conclusion might be uncertain because analyses were based on insufficient data – direct comparisons with placebo were not available and indirect comparisons with olanzapine had to be used instead. When it comes to QTc prolongation aripiprazole proved to be the most safe drug (OR 0.01, 95%CrI – 0.13 to 0.15). The least sedative of the investigated medicines was amisulpride (OR 1.42, 95%CrI 0.72 to 2,51) and it did not statistically differ from placebo. Aripiprazole was also close to placebo in that matter. Clozapine had the highest sedative potential (OR 8.82, 95%CrI 4.72 to 15.06).

Amisulpride in the treatment of psychosis with prominent or predominant negative symptoms

In 2018, a systematic literature review addressing the question of how effective second-generation neuroleptics might be in treatment of psychosis with primary predominant or prominent negative symptoms was published [3]. While patients with prominent negative symptoms are characterized as patients displaying a high degree of negative symptoms, which are accompanied by positive symptoms in any intensity, the definition of predominant negative symptoms includes strict condition of no or at most little positive symptoms present in clinical picture. The review included 21 randomized controlled trials (RCT) conducted in years 1989–2017 on a population of 3,451 patients with schizophrenia, schizoaffective or schizophreniform disorder. These RCTs assessed 34 antipsychotics, i.e., all atypical neuroleptics and a selection of first-generation ones. Medicines were used in any dose and in any form of administration, in monotherapy or in comparison to another antipsychotic or placebo. The measure of efficacy was the change in scores of relevant scale for assessment of negative symptoms such as the PANS, SANS [23] or BNSS [24]. Additional variable for drug assessment was, among others, the shift in intensity of positive and depressive symptoms. About 67% of the population was male, mean age was 39 years and the median trial duration was 12 weeks (6–52 weeks).

4 studies comparing amisulpride in the dose of 50–300 mg to placebo confirmed that it was superior to placebo in eliminating predominant negative and depressive symptoms (study group = 590, *SMD* 0.47, 95%CI 0.23 to 0.71), but it did not surpass placebo in alleviating positive symptoms, probably because of the dose being too low for antipsychotic effect. It was the only agent out of these assessed and compared directly to placebo in this systematic review that unequivocally proved its benefits over placebo in treatment of patients with predominant negative symptoms. One study compared amisulpride to olanzapine (in dose of 5–20 mg) and showed no difference between the two in treatment of predominant negative symptoms. However, olanzapine in that study had no benefit over placebo in alleviating negative, depressive and even positive symptoms whatsoever. Amisulpride opposed to fluphenazine (mean dose of 100–210 mg vs. 4–9.6 mg), haloperidol (doses unknown) and ziprasidone (mean dose of 145 vs. 118 mg) had no beneficial effects in treatment of predominant negative symptoms but still in one small study it stood out as more efficient than fluphenazine in treatment of depressive symptoms (study group = 48, *SMD* – 0.78, 95%CI –1.37 to – 0.19). Antidepressant effect of amisulpride was statistically significant and distinguished this drug amid other neuroleptics. It might be linked to its antagonistic effect on 5-HT_7 receptors [25]. The fact that majority of studies proving superiority of amisulpride in treatment of depressive symptoms were sponsored by pharmaceutical companies should be mentioned here.

Amisulpride in particular situations – advanced age

The effectiveness of amisulpride prescribed according to its indications, i.e., in young adults and middle aged patients with schizophrenia with positive and/or negative symptoms, has been confirmed in many clinical trials. Less is still known about off label uses of the drug and its efficacy in atypical age groups. There are reports suggesting high effectiveness of the amisulpride in treatment of very late-onset schizophrenia-like psychosis (over 60 years of age) with persecutory delusions and multimodal hallucinations but without affective disorder or dementia.

Howard et al. [26] in their randomized double-blind trial showed that amisulpride was more effective than placebo in such a clinical situation. Patients were randomly allocated to three study groups. First one received amisulpride 100 mg daily for 24 to 36 weeks, second received amisulpride for 12 weeks and then placebo for 12 to 24 weeks. The third group had it the opposite way – first placebo was used for 12 weeks and then amisulpride for the remaining time. The measure of effectiveness was the change in BPRS scores and presence of extrapyramidal symptoms as measured with the Simpson and Angus scale [27]. Data of 92 patients has been analyzed. Mean age was 80.2 years (*SD* 6.9) and the symptoms duration exceeded 6 months. The difference in BPRS scores was statistically significant in favor of amisulpride after 4 weeks of treatment (6.7 points, 95%CI 3.2 to 10.3; $p = 0.0003$) and rose further up to 7.7 points (95%CI 3.8 to 11.5) in 12th week of treatment. In subsequent weeks, in the case of patients who switched from amisulpride to placebo, a regression of clinical effect was observed and BPRS scores increased. Although there were no statistical differences in score rise in the Simpson and Angus scale between placebo and amisulpride groups yet the latter had more extrapyramidal symptoms and serious adverse effects. Also in this group falls were more common than in placebo treated patients but the difference was not statistically significant. In authors' opinion, despite unfavorable adverse effects of 100 mg of amisulpride in this particular age group, still the clinical benefits of reduced positive symptoms were evident and outweighed the risks of treatment.

Apart from late-onset schizophrenia-like psychosis in old age, amisulpride is sometimes used in demented patients for alleviating positive symptoms and disrupted behaviors associated with the primary disorder. Similarly like in the case of late-onset psychosis, the dose is low (about 50 mg daily) and its efficacy seems encouraging even though side effects such as sedation, extrapyramidal symptoms or cardiovascular complications and falls are reported. The risk may be minimized under the condition that the older and thinner the patient is the lower the dose should be. According to Reeves et al. [28] amisulpride renal clearance of an 85-year-old individual might be even 54% lower than that of a 65-year-old one. Moreover, in the age range of 65–85 years amisulpride plasma concentration might be dependent on body weight: at the dose of 50 mg daily and 70 kg of body weight it increased with age from 30 to 85 ng/ml, and in the case of body mass of 50 kg – from 40 up to 120 ng/ml significantly exceeding the threshold for extrapyramidal symptoms [28].

Recapitulation

1. Amisulpride is more effective than haloperidol in inducing clinical remission or ≥50% symptomatic improvement in patients with first psychotic episode. It is equal to olanzapine and slightly below clozapine in that respect, yet it has no side effects of the two.
2. Amisulpride triggers weight gain but less than olanzapine and slightly more than aripiprazole.
3. In comparison to clozapine amisulpride rarely leads to sedation, no more than placebo.
4. In comparison to haloperidol amisulpride rarely induces extrapyramidal symptoms, no more than placebo.
5. Amisulpride increases prolactin release, much like risperidone and it might prolong QTc similarly like sertindole.
6. Amisulpride is significantly more effective than placebo and classic neuroleptics in treatment of depressive and predominant negative symptoms.
7. In low doses and cautiously amisulpride might be used (off label) in patients over 60 years of age with late-onset schizophrenia-like psychosis.
8. Expansion of amisulpride treatment of the first psychotic episode beyond 4th week despite unsatisfactory clinical response might be equally effective as switch to olanzapine, yet it might save patients' time still needed for the therapeutic effect of the new drug to emerge.

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