Supporting Information

The Personal Antipsychotic Choice Index

Introducing a tool for shared decision-making in selecting antipsychotic medication

Authors

Floor Anna van Dijk¹, Iris de Wit², Matthijs Blankers³, Iris Sommer⁴, Lieuwe de Haan⁵

Affiliations

¹AMC, Early Psychosis Department, Amsterdam, Netherlands
²AMC, Early Psychosis, Amsterdam, Netherlands
³Arkin, Research, Amsterdam, Netherlands
⁴UMC Utrecht Hersencentrum, Psychiatry, Utrecht, Netherlands
⁵AMC, Academic Psychiatric Centre, Early Psychosis Department, Amsterdam, Netherlands

Correspondence Address

Miss Floor Anna van Dijk, MD
AMC, Early Psychosis Department, Postbus 22660, Amsterdam, Netherlands, 1100 DD
Tel.: +31/208/913 600
Fax: +31/208/913 701
f.a.vandijk@amc.uva.nl
Supplement A

1. Weight gain

Q: How acceptable is it if you would gain weight due to your antipsychotic medication?

Considerations concerning the ranking:

We have mainly used the results of the meta-analysis of Leucht et al [1], the meta-analysis of Bak et al [2] who also examined duration of antipsychotic use, complemented with two Cochrane reviews on pimozide and zuclopenthixol [3,4], and effects of olanzapine on M3 receptor (increased the risk on weight gain and diabetes), a regular review [5] and a clinical trial for perphenazine [6]. We have not used the singular results of the CATIE trial, as they were incorporated by Bak et al [2]. Although Bak showed an increased risk on weight gain for haloperidol and first generation antipsychotics on the long term (up to 38 weeks), it was decided to rank haloperidol based on the study of Leucht et al because they excluded non-blinded studies. This implies that the rank order below is mostly based on relative short term effects of antipsychotic medication on weight gain (6 weeks after start).

For penfluridol, pimpamperone, flupentixole and sulpiride we have not been able to find clinical data, they have therefore been listed as 'ambiguous/insufficient'.

2. Sexual dysfunction

Q: How acceptable is it if you would experience less desire to make love or have problems to have an orgasm due to your antipsychotic medication? How acceptable would it be for you if your erection becomes less strong?

Considerations concerning the ranking:

Sexual dysfunction is related to increased levels of prolactin and is dependent on antagonism of several receptor systems [7]. Prolactin levels rise as a result of dopamine blockade in the hypothalamus-pituitary axis, where dopamine activity inhibits the release of prolactine. A second important factor is an antipsychotic’s capacity to pass the blood-brain barrier. The pituitary gland lies outside the blood brain barrier and is therefore impacted by peripheral active metabolites of antipsychotics. Risperidone and amisulpride are medications that pass the blood brain barrier poorly and have a limited central-to-peripheral ratio, therefore they are associated with significant prolactin level increases [8].

In order to rank the agents, we have used the results of Leucht et al [1], complemented with results of two reviews [9,10]. Amisulpride has not been studied as consistently on clinical outcomes related to hyperprolactinemia as risperidone. Although several reviews [11],[9,12] claim amisulpride to have at least an equivalent effect on prolactine levels, they do not show an insightful comparison (with numerical data) to either haloperidol or risperidone. We have therefore decided to approach the claims conservatively and rank amisulpride together with haloperidol, until future clinical results state otherwise.
3. Drowsiness

Q: How acceptable is it if you get drowsy or slow due to your antipsychotic medication?

Considerations concerning the ranking:
Considerations are presented in table.

Adjustments in the algorithm value after running test scenarios 3 (see Results section)
Penfluridol was given the same value as haloperidol due to their similar biochemical compounds. Sulpiride, of which we only know that it does not block the H1-receptor [13], was given the value of the other non-H1-blocking agents aripiprazole and amisulpride, of which we did have a OR and NNH [1,14].

4. Sleep

Q: How acceptable is it if you sleep more or have more difficulty waking up due to your antipsychotic medication?

Considerations concerning the ranking:
Considerations are presented in table.

Adjustments in the algorithm value after running test scenarios 3 (see Results section)
Penfluridol was given the same value as haloperidol due to their similar biochemical compounds. Sulpiride, of which we only know that it does not block the H1-receptor [13], was given the value of the other non-H1-blocking agents aripiprazole and amisulpride, of which we did have a OR and NNH [1,14].

5. Extrapyramidal side effects

Q: How acceptable is it if you would experience muscle stiffness, tremors or restless movements due to your antipsychotic medication?

Note: EPS is a dose-related effect of antipsychotics.

Considerations concerning the ranking:
We have based the ranking primarily on Leucht’s meta-analysis of 2013. For missing data, we have used evidence concerning D2-receptor affinities of agents. Taken together with the notion that EPS are a dose dependent phenomenon, also occurring in rodents treated with agents with a low D2-affinity at high dosages [15] we consider D2-receptor affinities as an optimal estimation of the propensity to induce extrapyramidal side effects. Herewith we ignore the possible effects of 5HT2a-antagonism, intrinsic anticholinergic properties and multireceptortheories [16][17].
6./7./8./9. Anticholinergic effects

Q: How acceptable is it if you will...

... have blurred vision...
... be urinating less smoothly...
... get constipated more often...
...have a dry mouth more often...
due to your antipsychotic medication?

Considerations concerning the ranking:
Since various factors, such as smoking and concomitant medication, influence anticholinergic signaling in the human body, in addition to antipsychotic medication, the receptor affinity (Ki-value) of an antipsychotic agent does not necessarily represent the clinical anticholinergic effect or side effect. Muscarinic effects of antipsychotic agents can be assessed by the anticholinergic activity (AA). Chew et al. have described a model for an estimated dose-AA relationship of six antipsychotics [18]. Their procedure examines the amount of displacement of the muscarinic receptor antagonist titrated quinuclidinyl benzilate (3H-QNB) caused by compounds present in an individual's serum (or plasma). The effect of the antipsychotic agent was compared to a standardized atropine curve. Peripheral AA was correlated with serum levels of anticholinergic medications as well as AA in cerebral spinal fluid. The concentrations of atypical antipsychotics were based on typical serum or plasma drug levels and pharmacokinetic data were used to calculate an estimated dose-AA relationship [18]. We considered this to be to best step towards translation of K-values to clinical aspects. Clinical data to support these frameworks are incomplete due to underreporting in trials [19], and some reviews [5,20] do not give insight into the ranking of anticholinergic properties per agent, because they do not mention their sources with enough insight [19]. This makes comparison between antipsychotics difficult. The use of high dosages of FGA, mainly haloperidol and zuclopenthixol [21] flaws their results, as well as their inability to obtain information on concomitant use of anticholinergics [22].

We have decided to position clozapine, olanzapine and quetiapine on a relative distance to each other based on the anticholinergic action described by Chew, leaving the remaining agents in the 'rare' category. The cut off point for the 'rare' category was created by using the K-value of the M1-receptor of ziprasidone (an agent not included in our index). Chew et al mention two K-values for ziprasidone: the one found by Bymaster et al (300 nM) [23] and Schmidt et al (5100 nM)[24]. We have averaged these values to +/- 2700 nM. With regard to the lower limit of 300 nM and still a zero AA-dose, whereas quetiapine has a fixed affinity of 303 nM and a AA-dose relation of 1-15, we propose that the cutoff point must lie somewhat above 300nm (e.g. 400nM). Following this assumption, we have ranked pimozide (800 nM), lurasidone (>1000)[25] and perphenazine (1496), together with ziprasidone (2700 nM) and aripiprazole (6778 nM). Of penfluridoland pipamperone we have no data. They are grouped according to their comparability to haloperidol in M1-receptor affinity. Flupenxitol is given the same rank as quetiapine due to explicit mention of anticholinergic effects in the MedicaWiki initiative and the Summary of Product Characteristics. This means we have left out a review focusing on constipation from De Hert and colleagues [26]. Although they underscore the seriousness and high prevalence of constipation, they conclude that it is rarely studied and underreported and strengthen the need for further research. Constipation is thought to be caused via caused by antihistaminergic and antidopaminergic pathways [26]. If further clinical evidence emerges, constipation might be separated from the other anticholinergic effects.
10. Hypersalivation

Q: How acceptable would it be if you produced more saliva due to your antipsychotic medication?

Considerations concerning the ranking:
We have used the work of Ozbilen and colleagues[19], which provided numerical data.

Adjustments in the algorithm value after running test scenarios 3 (see Results section)
The algorithm values of rank 0 (meaning no data available) were given the value of the mean value of the item.

11. Nausea

Q: How acceptable is it if you would experience nausea more often due to your antipsychotic medication?

Considerations concerning the ranking:
It is unclear what mechanisms cause nausea associated with the use of antipsychotic agents (suggestions for clozapine include delayed gastric emptying due to anticholinergic effects or increased appetite due hypersalivation[27]). Ranking by receptor affinity therefore was not possible. Ranking was based on the information of Summary of Product Information. We subsequently used the significant results from Cochrane Reviews to subdivide aripiprazole and clozapine from the rest and to categorize olanzapine and pimozide as agents with less propensity to induce nausea.

Adjustments in the algorithm value after running test scenarios 3 (see Results section)
The algorithm values of rank 0 (meaning no data available) were given the value of the mean value of the item.

12. Dizziness

Q: How acceptable is it if you would experience dizziness more often due to your antipsychotic medication?

Note: dizziness is often a dose-related effect of antipsychotics.

Considerations concerning the ranking:
We have decided to rank the agents on their affinity for the adrenergic α1-receptor, being the associated receptor system of orthostatic mechanisms in, for example, clozapine [28]. Outcomes from clinical data, retrieved from Cochrane Reviews and reviews, encounter too much heterogeneity [29] and ambiguity [30].
Within the clinical trials, we then have given preference to Cochrane Review of Duggan et al. [31] on olanzapine. Only olanzapine shows significantly less dizziness than FGA after two years of treatment [31]. The confidence intervals on other antipsychotic agents from the study of Edwards et al [30] are broad and therefore more imprecise. The results of the Cochrane reviews on the other antipsychotic agents also have confidence intervals that surpass the 1.0 value. We decided to use the clinical data of olanzapine to create a cut-off point in distinguishing the α1-receptor affinities that are more likely associated with dizziness in clinical practice. Lurasidone is placed in the same category as olanzapine since the difference in Ki-value is small.

Adjustments in the algorithm value after running test scenarios 3 (see Results section)
The algorithm values of rank 0 (meaning no data available) were given the value of the mean value of the item.

13. Get tired more quickly

Q: How acceptable is it if you would get tired more quickly due to your antipsychotic medication?

Considerations concerning the ranking:
Fatigue is an under-researched topic, with heterogeneity between studies. Studies often only reported 'fatigue' when it occurred in at least 5% of the study population [32]. Results of a Cochrane review [32] show a trend for aripiprazole to be favored over other second generation antipsychotics. The large confidence intervals are probably due to the fact that per study arm few (<50) participants were included.

Since this is the only source, we have decided to rank aripiprazole as the antipsychotic drug with the least probability to induce fatigue.

Adjustments in the algorithm value after running test scenarios 3 (see Results section)
The algorithm values of rank 0 (meaning no data available) were given the value of the mean value of the item.

14. Blunted affect + Need for companionship

Q: How acceptable is it if you become flatter, less creative and less interested in companionship due to your antipsychotic medication?

Considerations concerning the ranking:
Despite this rather narrow description, feelings of emotional blunting have not been assessed in a similarly restricted manner. Therefore, as a general approach we searched for studies on general subjective well-being. It has been suggested that SGA, specifically, show an elevated level of subjective well-being than FGA [33]. 'Affect' and the feeling of being less creative are however not entirely covered by the traditional distribution of SGA being superior to FGA. Only a few clinical studies exist, that systematically researched 'affect': two double blinded RCT's [33,34] and one open label, semi-randomized clinical trial [35]. They concern olanzapine, Risperidone and haloperidol (and other FGA's). Olanzapine is favored over haloperidol in one of them [33], one other found no difference between olanzapine and risperidone[34]. De Haan et al showed that D2-occupancy between 60-70% is optimal for subjective well-being [36]. Next to this, a
naturalistic study focusing on positive and negative effect on ‘affect’ favors olanzapine over risperidone and haloperidol [37].

Meager evidence exists (derived from different study designs) that risperidone also causes secondary negative symptoms among which ‘avolition’. Mas et al. and Artaloytia et al [38] demonstrated this in RCT’s with healthy individuals after controlling for EPS and sedation. This was a single dose administration design. Also, an open-label study showed that olanzapine did better than clozapine and risperidone on ‘social integration’ [35]. However, these study designs do not reflect a systematic method and do not provide an explanation for the underlying cause.

Secondly, we propose a rationale for the occurrence of secondary negative symptoms. Secondary negative symptoms are suggested to be the logical result from treatment of positive symptoms by antipsychotic agents. By reducing cognitive biases seen in patients, like jumping to conclusions and having overconfidence in memory, patients experience increasing doubt and loss of decisiveness. Simultaneously, dampening hypersalience hence causes a subjective feeling of indifference towards stimuli and a loss of creativity and social contacts [8,39]. For ‘blunted affect’ we have used clinical results for ‘negative affect’ as circumstantial evidence. Subjective wellbeing is associated with D2-receptor binding. This is not a linear effect, as lower D2-binding is associated with more psychotic symptoms and results in a reduced motivational tone, whereas as higher D2-receptor occupancy causes less reward from stimuli, resulting in flattened emotions (due to blocking D2-receptors in the striatal region). This is supposedly explained by the fact that some agents bind looser to the D2-receptor (e.g. olanzapine) than others (haloperidol, but also risperidone)[37]. In addition to this mechanism, Meltzer and colleagues underline the importance of serotonergic receptor binding and relative low D2/D3 antagonism as a characteristic of ‘atypical antipsychotics’, but they do not provide robust clinical results pertaining to the effect on emotional well-being (depressive symptoms excluded), or more broadly, to secondary negative symptoms [16]. We therefore propose to rank the agents based on: 1. their D2-affinity being similar or less than that of dopamine (1.5 nM)[40] and 2. Their function as an agonist or antagonist of dopaminergic neurotransmission (e.g. aripiprazole).

15. Menstrual disorder (women only)

Q: How acceptable is it if your period occurred less often due to your antipsychotic medication?

Considerations concerning the ranking:
Antipsychotic-induced hyperprolactinemia is associated with menstrual disturbances [41]. Prolactin levels rise as a result of dopamine blockade in the hypothalamus-pituitary axis, where dopamine activity inhibits the release of prolactine. A second important factor is an antipsychotic’s capacity to pass the blood-brain barrier. The pituitary gland lies outside the blood brain barrier and is therefore impacted by peripheral active metabolites of antipsychotics. Risperidone and amisulpride are medications that poorly pass the blood brain barrier and have a poor central-to-peripheral ratio. As a result, they are associated with a significant increase in prolactin levels [8,42].

In order to rank the agents, the results by Leucht et al were used [1], complemented with results of two reviews [9,10]. Amisulpride has not been studied as consistently on clinical outcomes related to hyperprolactinaemia as risperidone. Although several reviews [9,11,12] claim amisulpride has at least equivalent effects on prolactine levels, they do not show an insightful comparison (with numerical data) to either haloperidol or risperidone. We have therefore decided to approach the claims conservatively and rank amisulpride together with haloperidol, until future clinical results state otherwise.
The same ranking has been used for item Sexual dysfunction.

**16. Effectiveness - overall change in symptoms**

**Q:** Antipsychotics differ slightly in how well they work. Some agents are more effective than others. How important is it for you that an antipsychotic reduces your psychotic symptoms as much as possible?

**Considerations concerning the ranking:**
We mainly used the data by Leucht and colleagues[1], complemented with a Cochrane review of penfluridol[43]. For flupentixol, sulpiride, pipamperone and zuclopentixol we could not identify clear data. They have been ranked ‘ambiguous/insufficient’.

**Adjustments in the algorithm value after running test scenarios 1 and 2 (see Results section)**
We have added the agents of which we had no numerical data, to the least effective rank of agents of which we did have numerical data. So it was avoided that ‘no data’ meant ‘no effect’. Also, to reflect the effectiveness of clozapine relative to the other agents, it got an algorithm value of 18 as compared to 6 for the second ranking group of olanzapine and amisulpride and 5 for the remaining agents in ranking group 3 (data not shown).

**17. Effectiveness - Depressive symptoms**

**Q:** How important is it for you that an antipsychotic improves your depressive symptoms as much as possible?

**Considerations concerning the ranking:**
We have used the data of Leucht and colleagues[14]. Since then, no randomized trial or review on this topic has been published. For haloperidol and zuclopentixole, we have used data from the Summary of Product Characteristics. Of the remaining first generation agents we could not identify clear data. They have been ranked ‘ambiguous/insufficient information’.

**Adjustments in the algorithm value after running test scenarios 1 and 2 (see Results section)**
The group of agents without numerical data got an algorithm value of 2, as compared to a 3 for the least effective group.

**18. Effectiveness - Memory and attention problems**

**Q:** How important is it for you that an antipsychotic improves your memory and concentration problems? Or how important is it that an antipsychotic does not further impair your memory and concentration problems?

**Considerations concerning the ranking:**
Disturbance in cognitive functions such as working memory, attention and executive function is caused by blockade of D2-, M1-, H1- and α1-receptors [44]. The effects of antipsychotic treatment have been meta-analysed by Désamericq et al [45] who found significant differences on subdomains (such as working memory and attention) of various agents compared to haloperidol. It would be most convenient to use these outcomes to rank the available agents to this report. However, it should be emphasized that open-label studies were included and that some studies used very high doses (>24mg) of haloperidol. Moreover in these studies different
cognition measurements and time intervals were used in comparison to controls generally lacked. It is therefore the question whether the results are representative and can be generalized for clinical use. Since there is no placebo comparison for haloperidol, we have decided to address a positive effect on these cognitive factors for olanzapine and quetiapine. Yet we leave a ‘neutral’ label to haloperidol and the rest, as to avoid that lack of proper data results in ‘negative’ properties.

It is unclear to what extent dosage of antipsychotics affect cognitive decline. It has been studied cross-sectionally [46,47] and also prospectively by Husa et al [48]. The latter could not make a distinction between FGA and SGA due to methodology. Until more clinical studies in a prospective study design and with a large enough sample size have been published, we remain with the ranking based on the results of Désamerique et al.

19. Ways of administration

Q: What kind of administration do you prefer?

1. Tablets daily
2. 1-2 tablets per week
3. Fluid administration daily (droplets and/or grinded and dissolved tablets)
4. Depot injection (ranging from every fortnight to every 6 weeks)

Considerations concerning the ranking:

Considerations are presented in table.

20. Additional questions concerning patient characteristics

Q: Have you ever suffered an epileptic seizure?

1. Yes (advice: reconsider group 3 and 4)
2. No

1. Epileptic seizure

Considerations concerning the ranking:

Data for ranking antipsychotic agents was retrieved from three published studies. Alper et al[49] reviewed data on report of seizure incidende retrieved from phase II and III trials (clinical and pre-clinical) of Basis of Aproval Reports USA. Only clozapine, quetiapie and olanzapine significantly showed a higher standardized incidence risk ratio. Secondly, we combined the results of Kumlien et al [50] and Lertxundi et al [51], who have used drug reaction databases of the WHO and Spain (Basque country). They counted the percentage of insults of the total spontaneously reported adverse drugs event per antipsychotic agent. This is an indirect and highly biased form of retrieving data, however it came closest to actual data of incidence. There have been no corrections for ways of administration or dosage. We judged the results of Kumlien as more important than those of Lertxundi due to their larger dataset. The findings of Kumlien were in line with those of Apler.

2. Wish to become pregnant and to lactate

Considerations concerning the ranking:

Limited research was available for ranking. Guidelines on pregnancy while using antipsychotic medication were studied, namely the RIVM (Dutch National Institute for Public Health and the Environment) and the GGZ Trimbos Instituut (a national mental health institute) guidelines[52]
based on a literature study of Gentile[53]. They conclude:
- Only prescribe antipsychotic medication to pregnant women on strict indication.
- If a psychosis occurs during pregnancy, and no antipsychotic drug is used, best prescribe first
generation antipsychotics
- Possible weight gain due to antipsychotic drugs olanzapine, quetiapine and risperidon may
increase on risk fetal malformations.
- If a woman becomes pregnant while using antipsychotic medication, it is advised to continue
the current drug instead of switching medication. The risk of switching is considered higher than
possible differences between agents in teratogenic or other effects.
- Consider to discontinue antipsychotic medication at the end of pregnancy to decrease risk on
extrapyramidal effects and insults on the neonate. This must be weighed against the risk on
recurrence of the psychosis.

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