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First-Generation Antipsychotics

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Synonyms

Classical antipsychotics; Classical neuroleptics; Conventional antipsychotics; Conventional neuroleptics; Major tranquilizers; Old antipsychotics; Old neuroleptics; Traditional antipsychotics; Traditional neuroleptics; Typical antipsychotics; Typical neuroleptics

Definition

Antipsychotics introduced to the market in USA before ▶ Clozapine (before 1989).

Pharmacological Properties

▶ First-generation antipsychotics (FGA) is a heterogeneous group of ▶ dopamine D_2 receptor antagonists with different chemical, pharmacological and clinical profile. Main clinical characteristic of the FGA is more ▶ Extrapyramidal Motor Side-Effects (EPSE), more frequent ▶ hyperprolactinaemia and less clinical efficacy if compared with the ▶ second-generation antipsychotics (SGA). There are, however, some exceptions from and inconsistencies in the definition above. For example ▶ amisulpride and ▶ risperidone, two SGA significantly increase prolactin levels and so some authors do not acknowledge hyperprolactinaemia as a good group differentiating factor. Moreover, clinical comparison of FGA and SGA gives ambiguous results. Today it is clearer that there are not sharp boundaries between FGA and SGA and maybe in the near feature more pertinent classification will be adopted.

Chemical Profile

Using chemical profile FGA can be classified as ▶ butyrophenones (e.g., ▶ haloperidol, ▶ bromperidol, ▶ benperidol, ▶ droperidol, ▶ pipamperone, ▶ spiperone, ▶ trifluperidol).

▶ Dibenzoxazepines: ▶ loxapine. ▶ Diphenylbuthylpiperidines: ▶ fluspirilene, ▶ penfluridol, ▶ pimozide. Au1
▶ Phenothiazines (e.g., ▶ chlorpromazine, ▶ clopenthixole, ▶ fluphenasine, ▶ metophenazate, ▶ metotrimeprazine, ▶ periciazine, ▶ perphenazine, ▶ prochlorperazine, ▶ promazine, ▶ promethazine, ▶ prothipendyle, ▶ thioridazine, ▶ trifluoperazine, ▶ triflupromazine. ▶ Substitued benzamides: ▶ sulpiride. *Other tricyclic antipsychotics*: ▶ carpipramine, ▶ clorotepine, ▶ oxyprothepine. ▶ Thioxantines (e.g., ▶ chlorprothixene, ▶ cisclopenthixole, ▶ flupenthixole, ▶ thiothixene, ▶ zuclopenthixole).

Many of these compounds are no more on the market.

Low and High Potency Antipsychotics

From clinical as well as pharmacological point of view FGA can be classified as *high-potency* and *low-potency* antipsychotics. Potency refers to their affinity to ▶ dopamine D2 receptors and the average therapeutic dose, compared with a 100 mg of chlorpromazine (so called ▶ chlorpromazine equivalent) (Baldessarini et al. 1988). Au2
The example of low-potency antipsychotics in light of ▶ evidence based medicine is chlorpromazine (Leucht et al. 2003). Low potency antipsychotics have been suggested to be more sedative than high potency antipsychotics but on the other hand induce less EPSE than high-potency antipsychotics. In sufficiently high doses, low potency antipsychotics are not, in principle, less effective than high potency antipsychotics such as haloperidol (Leucht et al. 2003). Low-potency antipsychotics induce more EPSE than clozapine, ▶ olanzapine and risperidone but not more than other SGA (Leucht et al. 2009). Low-potency antipsychotic are less sedative than clozapine, ▶ NNH (Number Need to Harm) 13 [7–220], but do not differ in this respect from other SGA (Leucht et al. 2009). Weight gain is similar to that after SGA and higher than after ▶ aripiprazole and ▶ ziprasidone (Leucht et al. 2009).

High-potency antipsychotics induce more EPSE than low-potency antipsychotics and SGA. The typical representative of this group is haloperidol. NNH for haloperidol to induce EPSE was between 2 for clozapine and 5 for ▶ zotepine (Leucht et al. 2009). On the other hand haloperidol was associated with less weight gain than most of

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SGA and was not different from aripiprazole and ziprasidone in this respect (Leucht et al. 2009). Haloperidol was significantly less sedating than clozapine (NNH 5 [3–14]), ▶ quetiapine (NNH 13 [8–20]), and zotepine (NNH not significant) but significantly more sedating than aripiprazole (NNH 33 [20–1,001]; (Leucht et al. 2009).

Efficacy of the FGA

The recent meta-analyzes concluded that the FGA as a group were less efficacious than some but not all antipsychotics from SGA (Leucht et al. 2009). In Leucht et al. (2009) meta-analysis 95 studies were included with haloperidol, 28 studies with chlorpromazine, five studies with perphenazine and less than five with other FGA. So results from this meta-analysis are more related to haloperidol or chlorpromazine than to other FGA. In the concrete, FGA was less effective in overall change of symptoms than amisulpride, clozapine, olanzapine, and risperidone; in the management of positive symptoms FGA were less effective than amisulpride, clozapine, olanzapine, quetiapine, and risperidone; in the management of negative symptoms FGA were less effective than amisulpride, clozapine, olanzapine and risperidone, and in alleviation of depression FGA were less effective than amisulpride, aripiprazole, clozapine, olanzapine and quetiapine (Leucht et al. 2009). FGA are less effective in long term treatment of schizophrenia than olanzapine (NNT 17 [8–100]), risperidone (NNT 11 [7–33]), and ▶ sertindole (NNT 14 [8–50]). FGA improve ▶ quality of life less than amisulpride, clozapine and sertindole (Leucht et al. 2009).

Naturalistic (Effectiveness) Studies

Results from real world effectiveness studies such as ▶ CATIE (Rosenheck et al. 2006), and ▶ CUtLASS (Jones et al. 2006) suggest that mid-potency FGA compounds would have been more appropriate, because they are less likely to cause EPSE and they are not associated with sedation and weight gain. The representatives of this group are perphenazine and sulpiride. Efficacy of SGA was not better than perphenazine on ▶ PANNS total score (Rosenheck et al. 2006), cognition (Keefe et al. 2007), cost (Rosenheck et al. 2006), quality of life, and psychosocial functioning (Swartz et al. 2007).

Another pragmatic trial (EUFEST) compared the effectiveness of SGA with that of a low dose of haloperidol (1–4 mg), in the first-episode schizophrenia (Kahn et al. 2008). This pragmatic trial found lower discontinuation rate with SGA than with haloperidol. However, symptom reductions were virtually the same (about 60%) in all groups. Despite the fact that the difference in discontinuation rates was the primary outcome variable one cannot definitively conclude that SGA are more efficacious than is the low dose haloperiddol in first-episode schizophrenia, since discontinuation rates are not necessarily consistent with symptomatic improvement.

Other Side Effects of the FGA

There are other typical side effects of the FGA than only EPSE and hyperprolactinaemia. These side effects are observed mainly in low-potency antipsychotics and are related to ▶ anticholinergic, ▶ antiadrenergic and ▶ antihistaminic activity. Anticholinergic activity of low-potency antipsychotics leads to dry mouth, blurred vision, difficulty passing urine, urinary retention, constipation, glaucoma and rarely ileus. Antiadrenergic activity can induce postural hypotension, reflex tachycardia, and sexual dysfunction (particularly erectile dysfunction). Antihistaminic activity is responsible for sedative effect and weight gain. Idiosyncratic side effects are: leucopenia or agranulocytosis, cholestatic jaundice, altered glucose tolerance, skin photosensitivity (sun block is important in sunny weather), pigmentation to skin or to eye, ▶ neuroleptic malignant syndrome. Some FGA can lower seizure threshold (i.e., chlorpromazine) or could prolong ▶ QT interval (chlorpromazine, droperidol, pimozide, thioridazine).

Cross-References

▶ Amisulpride
▶ Antiadrenergic
▶ Anticholinergic
▶ Antihistaminic
▶ Antipsychotics
▶ Aripiprazole
▶ Benperidol
▶ Bromperidol
▶ Butyrophenones
▶ Carpipramine
▶ CATIE
▶ Chlorpromazine
▶ Chlorpromazine Equivalent
▶ Chlorprothixene
▶ Cisclopenthixole
▶ Clopenthixole
▶ Clorotepine
▶ Clozapine
▶ CUtLASS
▶ Droperidol
▶ EUFEST
▶ Extrapyramidal Motor Side-effects
▶ Flupenthixole

- Fluphenasine
- Fluspirilene
- Haloperidol
- Hyperprolactinaemia
- Loxapine
- Metophenazate
- Metotrimeprazine
- Olanzapine
- Oxyprothepine
- PANNS
- Penfluridole
- Periciazine
- Perphenazine
- Perphenzine
- Phenothiazines
- Pimozide
- Pipamperon
- Prochlorperazine
- Promazine
- Promethazine
- Prothipendyle
- Quality of life
- Quetiapine
- Risperidone
- Second-Generation Antipsychotics
- Spiperone
- Substitued Benzamide
- Sulpiride
- Thioridazine
- Thiothixene
- Thioxanthenes
- Trifluoperazine
- Trifluperidol
- Triflupromazine
- Ziprasidone
- Zotepin
- Zuclopenthixole

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