# TREATMENT-RESISTANT SCHIZOPHRENIA: PHARMACOLOGICAL TREATMENT

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# What We Want to Review

- Definition
- What We Should Do If There is no Adequate Response to the 1st AP Drug
- Role of SGAs
- Clozapine
- Combination Strategies
- Augmentation Strategies

# Definition

- 20–30% of all patients with schizophrenia do not respond adequately to an initial antipsychotic trial.
- A uniform definition of treatment resistance in the pharmacotherapy of schizophrenia is not available.
- Most treatment guidelines require the failure of at least 2 antipsychotic (AP) trials with different compounds, including at least one second-generation antipsychotic (SGA), in adequate dose (chlorpromazine equivalents between 400 and 1000 mg/d) over a period between 2 and 8 weeks before treatment resistance can be assumed.

Hasan et al., 2012;
Suzuki et al., 2011 , 2012;
Buchanan et al., 2010; Lehman, et al., 2004; NICE, 2003;

# Definition …

Based on Kane criteria, patients have to be:

1. non-responsive to at least 3 periods of treatment in the preceding 5 years with AP agents (from at least 2 different chemical classes) at dosages equivalent to or greater than 1000 mg/d of chlorpromazine for a period of 6 weeks, each without significant symptomatic relief, and

2. without any period of good functioning within the preceding 5 years.

Kane et al., 1988;

# No Adequate Response to the 1st AP drug:

- Re-evaluation of the diagnosis of a schizophrenic disorder.
  - Severe personality disorders,
  - Mania or depressive disorders with psychotic features,
  - Brain tumors and encephalopathies,
  - Substance abuse,
  - Comorbidities such as affective disorders or OCD

Dold & Leucht, 2015;

# No Adequate Response to the 1st AP drug:

- Non-compliance can be considered as a major reason for non-response to Aps.
  - More than half of the patients do not take the prescribed medication correctly.
  - Plasma levels should be considered.
  - The use of long-acting injectable APs can sometimes be a possibility to rule out non-adherence.

Dold & Leucht, 2015;
Goff et al., 2010;

# No Adequate Response to the 1st AP drug:

- Was the AP dose sufficient and the treatment duration adequate?
  - Recommended doses
  - Patients with **first-episode** schizophrenia as well as **older** patients often require lower doses.
  - The onset of improvement may vary considerably.
  - International guidelines recommend a minimum medication period between 2 and 8 weeks until in case of insufficient response a change of the treatment strategy should be considered.

Hasan et al., 2012;
Buchanan et al., 2010; Lehman, et al., 2004;

# No Adequate Response to the 1st AP drug:

- The highest symptom reduction can be observed already within the first week of medication and then decreases consistently.
- In case of no symptom improvement within the first 2 weeks of treatment in adequate dose, no long-term response to therapy can be expected.
- Some studies even postulate that a statistically significant AP effect can already be observed within the first 24 h after administration of the medication.
- Analyses of clinical trials in treatment-resistant schizophrenia could display that in patients with a history of at least one non-response to AP treatment a significant symptom reduction occurs within the first 4 weeks.

Agid et al , 2003;
Leucht et al., 2007;
Kapur et al., 2005;.

# No Adequate Response to the 1st AP drug:

- Side effects of antipsychotics can mask treatment response.
- For example, akathisia can be misinterpreted as mental agitation or parkinsonism may mimic schizophrenic negative symptoms.

# No Adequate Response to the 1st AP drug:

- Were sufficient plasma levels achieved?
  - Currently, there is no convincing evidence for a clear relationship between drug concentrations in the blood and AP response.
  - An exact dose titration guided by Therapeutic Drug Monitoring (TDM) may be justified for clozapine, at best.
  - Plasma level measurements may be useful in clinical practice in case of inefficacy of the medication or occurrence of severe adverse effects even at low doses.

Gardner et al., 2010;

# No Adequate Response to the 1st AP drug:

- Applying TDM, metabolization abnormalities as well as insufficient compliance of the patient can be identified or excluded as reason for treatment failure.

- Polymorphisms in the cytochrome P450 enzyme system can be also detected.

- '**ultrarapid metabolizer**', (1% of the population) vs. '**poor metabolizer**', (5% of the population)

Dold & Leucht, 2015

# No Adequate Response to the 1st AP drug:

- Dose increase or switching of the AP drug
  - Two strategies that are often used in clinical routine care are:
    - A dose increase of the current administered AP agent (dose escalation, high dose treatment)
    - A switch to another, new AP drug,

Dold & Leucht, 2015

# No Adequate Response to the 1st AP drug:

- A daily dose more than 800–1000 mg chlorpromazine equivalents (or even lower) dose of FGAs does not improve AP efficacy but is associated with an increased incidence of especially extrapyramidal adverse effects.19

- Although dose escalation cannot be advised generally, individual patients may respond to a high-dose or even off-label treatment.

- Applying blood monitoring of drugs raises the possibility of identifying patients that could probably benefit from high-dose medication.18

Davis & Chen, 2004;
Hiemke et al., 2011;

# No Adequate Response to the 1st AP drug:

- Switching the AP drug.
  - There is insufficient evidence for clear therapeutic recommendations with regard to a switching strategy.
  - Even if only moderate-to-low response rates can be expected, some patients appear to benefit from a switch of medication.
  - From an evidence-based perspective, a slight advantages of this strategy compared to a high-dose treatment with antipsychotics.

Dold & Leucht, 2015;

# No Adequate Response to the 1st AP drug:

- **Crossover titration:**

  For switching the AP drug, it is recommended to taper off the dose of the first AP gradually while simultaneously the dose of the second one is titrated up gradually to its target dose

- **Overlap and taper :**

  Alternatively, the dose of the first AP can be maintained at the same dose while the dose of the second compound is increased gradually to a therapeutic level and only then the dose of the first agent will be decreased

Dold & Leucht, 2015;
Hasan et al., 2012;
Leucht et al., 2013;

# No Adequate Response to the 1st AP drug:

- Choose a new compound with a different receptor binding profile

- In the 'Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)' trial, non-responders to perphenazine benefited significantly more from a switch to olanzapine or quetiapine compared to risperidone; probably because both perphenazine and risperidone are characterized by high antidopaminergic properties.

# Pharmacotherapy with clozapine

- A large number of clinical trials were conducted to elucidate which AP is characterized by the highest AP efficacy.
- The SGAs clozapine, amisulpride, olanzapine and risperidone appear to be slightly more effective in terms of AP efficacy than the other AP drugs.
- With the exception of clozapine the differences in effect sizes are small.

Leucht et al., 2009;
Leucht et al., 2013;

# Pharmacotherapy with clozapine

- In a network meta-analysis comprising 212 randomized trials and a total of 43 049 patients with schizophrenia, clozapine achieved the highest effect size in terms of AP efficacy followed by amisulpride, olanzapine and risperidone.

- Interestingly, studies with therapy-resistant patients were excluded in this analysis and clozapine was superior even in non-resistant participants.

- The superiority of clozapine stems mainly from comparisons with FGAs rather than SGAs.

Leucht et al., 2013;

# Pharmacotherapy with clozapine

- Clozapine is currently classified as first-line treatment in treatment-resistant schizophrenia.

- Clozapine resulted superior to other SGAs in a phase II study of the CATIE trial and in the 'Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 2)' when analyzing schizophrenic symptom improvement.

Gardner et al., 2010; Agid et al. 2003; Leucht et al. 2007; Lewis et al., 2006;

# Pharmacotherapy with clozapine

- Clozapine remains the gold standard and mainstay in the treatment of refractory schizophrenia.

- Due to its risk profile , clozapine may be used only after at least 2 failed previous treatment attempts with 2 other different AP in adequate dosage and duration.

- In clinical practice, mainly sedation, weight gain and hypersalivation may hamper the compliance of patients.

Hasan et al., 2012;
Buchanan et al., 2010; Lehman, et al., 2004;

# The Role of Other SGAs in Treatment-Resistant Schizophrenia

- An ambiguity remains regarding the status of other APs in treatment-resistant conditions.
- Significant effect sizes were also found for the SGAs risperidone, olanzapine and amisulpride.
- Some treatment guidelines recommend explicitly a treatment preferably with olanzapine or risperidone.
- In clinical trials with treatment-resistant patients, both compounds were not significantly inferior in direct comparison to clozapine and were able to achieve higher effect sizes compared to FGAs.

Leucht et al., 2009;
Leucht et al., 2013;
Hasan et al., 2012;
Leucht et al. 2013b;

# Combination strategies

- Defined as the simultaneous administration of 2 drugs of the same group such as 2 APs.
- A small but statistically significant superiority of the combination treatment compared to placebo has been shown.
- Other meta-analysis by Sommer et al, (2012) stratified according to the various compounds combined with clozapine, a significant positive effect was determined only for sulpiride (based on a single trial) but not for amisulpride, aripiprazole, risperidone and haloperidol.
- Barbui et al (2009) found a significant superiority of clozapine combination with SGAs only for randomized open studies but not for double-blind trials.

Taylor et al., 2015;

# Combination strategies

- Clozapine is the most evaluated AP drug regarding combination treatments.
- The most frequently investigated single combination is that of clozapine with risperidone.
- From a pharmacological point of view, it seems auspicious to combine APs with low antidopaminergic properties such as clozapine with APs that are characterized by a particularly strong affinity to dopamine receptors, such as amisulpride, sulpiride, haloperidol or risperidone.

Dold & Leucht, 2015;

# Combination strategies

- Cotreatment with aripiprazole can reduce AP-induced metabolic adverse effects as well as elevated serum prolactin levels.

- Efficacy, drug interactions and the occurrence of adverse effects should be closely monitored and, in case of inefficacy of the combination strategy, monotherapy should be considered again.

- In particular, the risk of metabolic side effects, and discontinuation may increase significantly by administering AP combinations.

Fleischhacker & Uchida, 2012;
Gallego et al., 2012;

# Augmentation strategies

- Augmentation treatment means the concomitant use of 2 drugs of different classes, for example the coadministration of an AP drug with an antidepressant, mood stabilizer or BZD.

- Augmentor of APs without demonstrating convincing efficacy in treating schizophrenic symptoms: acetylcholinesterase inhibitors, β-blockers, carbamazepine, lithium, valproate and memantine.

- Although BZDs may be indicated in short-term treatment of acutely agitated patients, there is no evidence for the use of BZDs as long-term adjunctive treatment to improve psychotic symptoms.

Leucht et al., 2013a;
Dold et al., 2013;

# Augmentation strategies

- Sommer et al. (2012) found in their meta-analysis a significant positive effect of lamotrigine augmentation in clozapine-resistant schizophrenia but this effect disappeared in a sensitivity analysis after exclusion of an outlier study with high effect size and small sample size.

- Similarly, a significant positive effect of topiramate on schizophrenic positive symptoms diminished after removal of an outlier study.

- Very recent meta-analyses support augmentation with aspirin or other drugs with effects on the immune system, but these findings are in our opinion not yet ready for transfer into practice.

Sommer et al. 2012;
Sommer et al. 2014;

# Augmentation strategies

- There is no sufficient evidence to advise the general use of pharmacological augmentation strategies in treatment-resistant schizophrenia.
- A possible increase of adverse effects and drug interactions must be considered.
- Augmentation strategies should be regarded preferable for the treatment of specific target symptoms.
- Augmentation and combination treatments should be discontinued in case of inefficacy and AP monotherapy should be sought again.

Dold & Leucht, 2015;

# Summary

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