CINP SCHIZOPHRENIA GUIDELINE

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Grades of recommendations

A) Systematic review of randomized controlled trials or single randomized controlled trials
B) Systematic review of case control or cohort studies, or single case control or cohort studies
C) Case series, case reports, expert opinion, good clinical practice

We indicated with minus (-) signs whether despite available evidence we considered a given evidence level as borderline. The recommendations are in part based on a previous publication (Leucht et al., 2011), which has been updated and amended, but other passages remained unchanged.

A) TREATMENT OF AN ACUTE EPISODE OF SCHIZOPHRENIA

1. Criteria for choice of drug in acutely ill patients

a) Evidence of prior response to the same drug (C)

b) Avoid side-effects experienced with a drug in the past (C)

c) Planned mode of administration (C)

d) Side-effect profiles (A)

e) Small differences in antipsychotic efficacy (A)

f) Patient's preference for a specific drug determined by shared-decision making (A-)

g) Cost (C)

Justification:

ad a) If a patient has responded to an antipsychotic in the past this could be a predictor that he will respond to it again.

Ad b) Similarly, side-effects experienced in the past might be avoided by choosing another antipsychotic.
Ad c) If it is clear that a patient will receive a depot for maintenance treatment, choosing the oral form of the same drug can facilitate the later transition.

Ad d) Antipsychotics differ largely in side-effects (e.g. Leucht et al., 2013a; Leucht et al., 2009b). This also applies to long-acting injectable formulations of antipsychotics (McEvoy et al., 2014), which have side-effect profiles that closely resemble their oral versions (Fleischhacker et al., 2014). Table 1 provides an overview of the side-effect profiles of second-generation antipsychotic and the two prototypal first-generation antipsychotics haloperidol and chlorpromazine that might be used for the selection (Table 1).

Ad e) Meta-analyses found that some antipsychotics (clozapine, amisulpride, olanzapine, risperidone, (zotepine, paliperidone)) are somewhat more efficacious than others (Davis et al., 2003; Geddes et al., 2000; Leucht et al., 2009b). We highlight that apart from clozapine, which is restricted to treatment resistant patients, the superiorities were small and overall smaller than differences in the major side-effects.

Ad f) A variety of antipsychotics with different profiles is available. Some patients may want to avoid weight gain, others EPS or sexual side-effects, and again others might even want an only slightly more efficacious drug, irrespective of side-effects. We, therefore, recommend involving patients in the decision where feasible. Involving patients in the decision making progress is simply good clinical practice and may also improve compliance and long-term outcome – despite limited evidence there is at least one RCT suggesting positive effects on some outcomes (Hamann et al., 2007; Hamann et al., 2003).

Ad g) New antipsychotics are generally more expensive than older ones, but medication cost will differ between countries (e.g. newer antipsychotics become generic and usually cheaper at some stage) and settings. Therefore, no general statement can be made, but it certainly is a criterion for choice, as well.

2. Patients should be started on monotherapy with one drug (A)

Justification:

Polypharmacy can be associated with more side-effects and drug-drug interactions (Fleischhacker and Uchida, 2014). If two antipsychotics are started simultaneously it is difficult to disentangle which drug was efficacious, making it difficult to stop one of them once the patient has responded. Similarly, if side effects emerge, it is unclear, which medication or dose may need to be changed. Moreover, non-adherence is an enormous problem in schizophrenia, and the more drugs patients receive the more difficult it could be to comply with the regimen. There is no randomized evidence supporting the immediate start of combination therapy apart from a meta-analysis of Chinese trials that was mainly based on combinations of clozapine with other antipsychotics (Correll et al., 2009b), but in most countries clozapine is restricted to refractory patients. The rationale of combining antipsychotics is also limited by the fact that they all have the same main putative mechanism of action for psychosis, which is dopamine blockade (Goodwin et al., 2009).

3. Factors that need to be checked before non-response is assumed

a) Is the underlying psychiatric diagnosis correct and have psychiatric comorbidities, including substance abuse, as well as somatic comorbidities or somatic causes been adequately excluded? (C)

b) Have ongoing environmental or psychological stressors as a cause of non-response been excluded? (C)

c) Has response been measured objectively and quantitatively? (C)

d) Do side effects mask a response, mimic non-response? (C)

e) Has a sufficient dose been given? (A)

f) Was treatment given for an adequate duration (change of treatment only if less than minimal response despite at least 2-4 weeks with full dose)? (A)

g) Has compliance been checked/optimized? Optimize compliance-transparency by obtaining antipsychotic plasma-levels (C), or use of liquids or rapidly-dissolving tablets (especially in inpatients (C)), or depot drug (B).

h) Has an adequate plasma level been reached? If not (and therapeutic windows are available), check for cytochrome-P-450 polymorphism, effect of smoking or drug-drug interactions. (C)

Justification:

Ad a) For example, a psychotic depression/mania or severe personality disturbances can be

difficult to distinguish from schizophrenia. Similarly, many neuropsychiatric disorders such as encephalitis, neurosyphilis can mimick schizophrenia and heavy cannabis or alcohol abuse can explain non-response, as well.

Ad b) Ongoing severe stressors, such as homelessness, poor housing, severe financial difficulties, violence and personal conflict will interfere with the therapeutic effect of antipsychotic medication.

Ad c) Unfortunately, the assessment of response to antipsychotic medication often remains subjective and qualitative, resulting in ambiguous judgments. Response should be assessed in a standard fashion, ideally both qualitatively as well quantitatively using validated psychometric instruments (e.g. at least the CGI or the 8 PANSS items on which the remission criteria by Andreasen et al., 2005 are based).

Ad d) For example, akathisia can be confused with psychotic agitation or parkinsonism can mimic negative symptoms. Such confounding factors need to be ruled out and addressed before non-response is established.

Ad e) It should be checked whether the patient has received a dose within the recommended dose range. If possible, a dose at the upper limit of these ranges should be given before non-response is determined. Guidelines differ slightly in their recommendations. The numbers presented below are according to those of the International Consensus Study on Antipsychotic Dose (Gardner et al., 2010). Equivalent dose tables based on various methods have also been published elsewhere (Leucht et al., 2015a; Leucht et al., 2014). We emphasize that the optimum doses for newer antipsychotics have been established by appropriate dose finding studies, while much less is known about the optimum doses of older antipsychotics, including haloperidol one of the few older drugs for which a real dose/response study exists (Zimbroff et al., 1997). For haloperidol, for example, a Cochrane review (Waraich et al., 2002) concluded that doses up to 7.5 mg/day should usually be sufficient in uncomplicated patients with schizophrenia. While there is evidence for some of these medications that doses below this range (e.g. risperidone 1 mg/d; aripiprazole 2 mg/d) are ineffective; there is no good randomized evidence that doses higher than these ranges show a further increase in response (also see paragraph on increasing the dose in case of non-response below). The main concern on the higher end is an increase in side-effects and cost.

Table 2: Dose recommendations for antipsychotic drugs (Gardner et al., 2010)

	Starting dose	**Target dose**	**Maximum dose**
Drug	**Median**	**Range**	**Median recommendation**
Amisulpride	100	400–800	1000
Aripiprazole	10	15–30	30
Asenapine	n.i.	10-20	n.i.
Benperidol	0.5	1.0–3.0	3.5
Chlorpromazine	100	300–600	800
Clopenthixol	17.5	22–90	138

Chlorprothixene	50	200–400	600
Clotiapine	40	100–120	240
Clozapine	25	200–500	800
Droperidol	3	4.5–8.8	12
Flupenthixol	3	5.0–12	18
Fluphenazine	3	5.0–15	20
Haloperidol	3	5.0–10	20
Iloperidone	n.i.	12-24	24
Levomepromazine	50	150–400	500
Loxapine	17.5	20–100	200
Lurasidone	n.i.	40-160	160
Mesoridazine	25	100–250	400
Methotrimeprazine	50	100–300	500
Molindone	22.5	50–188	225
Olanzapine	5	10–20	30
Oxypertine	40	80–150	200
Paliperidone	3	6.0–9.0	12
Pericyazine	20	20–50	60
Perphenazine	8	12–24	42
Pimozide	2	4.0–6.0	10
Prochlorperazine	15	15–48	90
Quetiapine	100	400–800	1000
Risperidone	2	4.0–6.0	8.5
Sertindole	4	12–20	22
Sulpiride	100	300–600	1000
Thioridazine	88	200–500	800
Thiothixene	6	15–30	40
Trifluoperazine	5	10–20	35
Trifluperidol	1	1.0–3.0	3
Triflupromazine	10	22–125	150
Ziprasidone	40	120–160	200
Zotepine	50	100–300	400
Zuclopenthixol	20	20–60	80

All doses are presented in mg/day. Target doses were defined as the “doses considered to be effective and acceptably tolerated by most patients”, and maximum doses as the “dose at which no further benefits are expected if exceeded or at which when exceeded the harms usually outweigh the benefits in patients”. N.i. = not indicated. Please note that for first-episode patients and elderly patients usually lower doses are sufficient (see respective passage of this algorithm)

Ad f) The onset of response to treatment of individual patients is highly variable. Nevertheless, recent meta-analyses rejected the long-held hypothesis that there is a general ‘delay of onset of action’ of antipsychotic drugs of several weeks. The largest part of the drug effect occurred in the first week and got consistently smaller thereafter (Agid et al., 2003; Leucht et al., 2005). An early response pattern has also been shown for clozapine (Sherwood et al., 2012). Moreover, several studies suggested that patients who had not improved at two weeks were unlikely to respond to

the same antipsychotic at a later stage (Ascher-Svanum et al., 2007; Chang et al., 2006; Correll et al., 2003; Jager et al., 2009; Kinon et al., 2008a; Leucht et al., 2007a; Leucht et al., 2008; Lin et al., 2007). While one study (Lambert et al., 2009) was not consistent with the other evidence, and while analyses in first-episode populations were also not consistent with the findings of multiple-episode populations (Gallego et al., 2011; Schennach-Wolff et al., 2010), a diagnostic test meta-analysis of 32 trials confirmed the predictive value of less than 20% PANSS/BPRS total score reduction at two weeks as a predictor of non-response at six weeks (Samara et al., 2015). Still, little evidence is available that switching, a major dose increase or combination treatment is effective (see below). We, therefore, recommend, at least in multi-episode patients, unless the clinical situation demands an earlier intervention, that a 2- to 4-week antipsychotic trial at a therapeutic dose in the upper dose range is appropriate before considering a specific antipsychotic ineffective for a patient. The notion "at a therapeutic dose in the upper dose range" is important, because some drugs, in particular clozapine, require slow titration. We nevertheless feel that previous claims to try clozapine for at least six months were mainly based on an uncontrolled case series (Meltzer et al., 1989) although continued treatment with clozapine beyond 4 weeks leads to an increased likelikhood of achieving response (Kane et al., 2001).

Ad g) In the case of suspected compliance problems these can be addressed by switching to liquid medication or rapidly dissolving tablets and/or supervised drug intake. Depot medication is another option (see paragraph on depot antipsychotics below). Plasma-levels can help in determining non-compliance and in monitoring compliance. The use and the determination of a patient's Cytochrom-P-450 status (Muller et al., 2013) can also be useful in certain circumstances as detailed below.

Ad h) The relationship between plasma-levels and response to antipsychotic drugs is not strong enough to recommend the titration into therapeutic concentration windows. Hiemke et al., 2011 present an overview of the levels for different psychotropic drugs. It might be most useful for clozapine (Buchanan et al., 2010). If available, antipsychotic plasma level measurements can be indicated in the following situations:

- Suspicion of non-compliance

- Lack of response in spite of taking usually sufficient doses to rule out ultra-rapid excessive metabolization of the antipsychotic due to a polymorphism of the cytochrom-P450 enzyme system (Muller et al., 2013).

- Pronounced side effects despite the administration of a usual dose to rule out „poor metabolizers" due to too little production of cytochrom-P450 enzymes.

- The genetically determined metabolizer status, medication interactions, smoking, etc. which can also lead to elevated or lowered plasma levels via effects on the Cytochrom-P450 system.

4. **Initial non-response: The antipsychotic may be switched (A-) or the dose may be increased beyond the officially indicated range (C). The evidence supporting both strategies is very limited. If the dose is increased, it should be decreased back to the original dose in case of lack of effect of the higher dose (C). If the drug is switched, choose an antipsychotic with a**

different receptor binding profile than the previous one (A-). Also consider the general selection criteria described above (see 1).

Justification:

The evidence for both strategies is limited with a certain advantage for switching.

a) Justification: Switching the drug (Leucht et al., 2015b): One trial found that when patients, who had at best minimally improved after two weeks treatment with risperidone, were switched to olanzapine, their outcome was significantly better than that of those who stayed on risperidone, but the difference was small (Kinon et al., 2010). In patients who had not responded to a four week trial of 20mg/day fluphenazine, Kinon et al., 1993 found no difference between a) continuation with fluphenazine 20mg/day (control group), b) dose increase to fluphenazine 80mg/day or switch to haloperidol 20mg/day.The limitation was the switch to a very similar high-potency antipsychotic (from fluphenazine to haloperidol, the study was conducted before more different newer drugs were available) and the fluphenazine dose in the run-in phase which is nowadays considered to be a high dose. Shalev et al., 1993 and Suzuki et al., 2007, randomized patients to three different antipsychotics. Non-responders were re-randomised to one of the two remaining two antipsychotics. If they failed to respond again they were switched to the remaining antipsychotic. At the end of both studies, the majority of participants had responded, but both studies had the major limitation of not having a control group that stayed on the initial drug to rule out that the improvement was simply an effect of time. In two small studies Hatta et al., 2011 randomised non-improvers to two weeks of treatment with risperidone/olanzapine to either staying on the same drug or switching to the other one. Switching did not lead to higher response rates, but the authors emphasize that the trials were underpowered. In a post hoc analysis of CATIE phase 1, patients taking olanzapine or risperidone before entering the trial stayed on treatment longer if they were assigned to stay on the same treatment (Essock et al., 2006). I.e. for these groups 'sticking' was better than 'switching'. One reason might have been that some of the chronic patients in CATIE were relatively stable at baseline and might have been destabilized by a switch. In summary, the evidence for switching antipsychotics is limited, but stronger than that for dose increase (see next chapter).

A later CATIE phase provides suggestive information on how to choose a new antipsychotic when switching. Stroup et al., 2007 analyzed those 114 participants who had received perphenazine in CATIE phase 1, but discontinued it. Participants who were randomized to quetiapine or olanzapine in phase 2 stayed on the antipsychotic longer than those randomized to risperidone. A possible explanation is that because perphenazine and risperidone have similar receptor-binding profiles, switching from one to the other has little effect. Thus, if the antipsychotic drug is changed, it is reasonable to choose a compound with a different receptor-binding profile. This pragmatic recommendation is based on the underlying assumption that patients who have not responded to one drug might respond to or have less adverse effects on another drug with a very different pharmacologic profile. If there has been non-response to at least two antipsychotics, we recommend a trial of clozapine (See below).

b) Substantial dose increase: The aforementioned study by Kinon et al., 1993 showed no incremental efficacy of increasing fluphenazine 20mg/day to 80mg/day. McEvoy et al., 1991 randomized patients who had not responded to neuroleptic threshold doses of haloperidol (mean 2.3 mg/day) to either continuation of threshold doses or doses up to 10 times. The dose increase was not associated with better efficacy. Hatta et al., 2012 found no significant difference between switching to olanzapine and increasing the risperidone dose in two week non-improvers to risperidone (Hatta et al., 2012). Kinon et al., 2008b found no efficacy difference between 10mg/day, 20mg/day and 40mg/day olanzapine in patients with suboptimal response to previous treatment. 40mg/day olanzapine was only somewhat (but statistically significantly) better in a severely-ill subgroup. Two small RCTs did not find a superiority of high dose quetiapine (1200mg/day) compared to 800mg/day and 600mg/day (Honer et al., 2012; Lindenmayer et al., 2011). A meta-analysis of the currently available studies also showed no superiority of increasing the dose in non-responsive patients (Dold et al., 2015). Thus, the evidence supporting doses above the therapeutic ranges is scarce, but as there are so few RCTs more trials are clearly needed. Some individuals respond only to very high doses and such a history should be considered, these may be also ultra-rapid metabolizers. We strongly discourage excessive doses as a general strategy. It is very important that if a dose increase beyond the optimum doses was not effective, the dose is again reduced to previous levels. Patients should never be exposed to unnecessarily high doses of antipsychotic medication.

5. Drugs should be switched applying an "overlap and taper" or "cross-over" strategies, especially when switching from sedating to less sedating and from high affinity full dopamine antagonists to lower affinity dopamine antagonists or to a partial agonist (A)

Justification:

Different switch strategies have been used clinically, but only few have been compared head to head. "Stop-start" means that the original drug is stopped abruptly and the next one immediately started. "Cross-over" means that the original drug is gradually tapered while the dose of the next one is gradually increased. "Overlap and taper" means that the full dose of the original drug is maintained until the next one reaches its therapeutic dose. Only then is the original drug gradually tapered. Finally, in one study the original antipsychotic was tapered entirely and the next drug (olanzapine) was started only one week afterwards (Kinon et al., 2000). This strategy was slightly less efficacious and carries a risk of loss of efficacy and of rebound symptoms, but should theoretically be associated with the fewest side-effects. There are theoretical pros and cons of the other three strategies: "Stop-start" is fast, but there could be withdrawal effects from the discontinuation of the original antipsychotic and efficacy problems, as the following drug has not developed its full effects. In "cross-over" there may be drug-drug interactions and a point when no drug develops its full efficacy. "Overlap and taper" is the safest procedure efficacy-wise, but if antipsychotics have similar adverse effects, these could be additive, and sometimes patients might be doing better when they have the combination making it difficult to stop one drug. Initial studies of second-generation antipsychotics and an earlier meta-analysis (Remington et al., 2005) did not find significant differences between abrupt or gradual initiation of the new antipsychotic, or between abrupt or gradual discontinuation of the pre-switch antipsychotic (Remington et al.,

2005). However, a recent, larger meta-analysis found that abrupt stopping of the prior antipsychotic and abrupt starting of the new antipsychotic were each associated with significantly greater all-cause discontinuation than gradual switches. Moreover, cross over and overlap and taper procedures were associated with significantly lower all-cause discontinuation rates than little or no overlapping strategies (Correll et al., 2011). The advantage of overlapping switches was strongest when switching to aripiprazole or ziprasidone. Although there were no differences in PANSS total scores between the switch strategies, patients were relatively stable and patients who dropped out were often not available for psychopathology ratings. Thus, if time allows and when a switch is performed to reduce adverse effects, we would recommend "cross-over" or "overlap and taper". However, in acutely exacerbated patients or when speed of the switch is important, "stop-start" switching is also possible, especially when concomitant benzodiazepines can be used to mitigate any relevant rebound or withdrawal effects and when the initial drug has not been taken for more than two weeks. In addition, it must also be considered that these recommendations do not hold true for all drugs. For example clozapine needs to be titrated slowly. And when the original medication is a depot antipsychotic, it can simply be stopped because due to the long half-life it will take considerable time until it is washed out. Conversely, if the new medication is a depot, in some circumstances (e.g. risperidone and aripiprazole long-acting injectable) the oral medication needs to be continued past the initiation of the depot, as the latter takes a few weeks to establish therapeutically efficacious levels.

6. **Clozapine is the antipsychotic of choice for treatment resistant patients (A). It should be used if at least 2 other antipsychotics given in sufficient doses (see above) and duration (at least 4 weeks) have failed (C).**

   Justification:

   Clozapine has been shown to be significantly more efficacious than first-generation antipsychotics for treatment resistant patients in single RCTs and meta-analyses (Kane et al., 1988; Leucht et al., 2009b; Rosenheck et al., 1997; Wahlbeck et al., 1999). Although the evidence compared to second-generation antipsychotics is less clear (Leucht et al., 2009d), it remains the drug of choice for these people. The recommendation that at least 2 other drugs should have been used before clozapine is started is a pragmatic one doing justice to the increased risk of agranulocytosis and related increased blood test requirements, as it is implemented in most labels.

7. **Combinations of antipsychotics: No strong evidence supports the use of polypharmacy over monotherapy for efficacy (A-). A reduction of hyperprolactinemia when adding aripiprazole to haloperidol or risperidone and the reduction of body weight, lipid and glucose levels when adding aripiprazole to clozapine or olanzapine (but not when adding it to quetiapine or risperidone) has been shown (A).**

   Justification:

   Various systematic reviews have examined the effects of combining antipsychotic drugs. Most of them found a small, but statistically significant superiority of the combining

antipsychotics, but the evidence was never convincing. Correll et al., 2009b meta-analysed all combinations of antipsychotics irrespective of the drugs used. Combination therapy was more efficacious than monotherapy, but the effect was mainly driven by Chinese trials, in which combination treatment was given right from the start, rather than only in the case of non-response. Three other systematic reviews specifically examined combinations of clozapine plus another antipsychotic: Sommer et al., 2011 who analysed each antipsychotic added to clozapine separately found only sulpiride augmentation to be effective, but this finding was based on a single trial. Taylor et al., 2012 analysed all antipsychotics added to clozapine as one group and found a small but statistically significant superiority of the combination strategy. In another meta-analysis by Barbui et al., 2009, the same combination strategy was, however, only superior to clozapine monotherapy in open RCTs, but not in double-blind ones. In choosing an antipsychotic that is added to clozapine, it might be considered that clozapine has a low affinity to dopamine receptors. Therefore, drugs that are selective for dopamine receptors, such as amisulpride or sulpiride, but also aripiprazole (mainly a partial dopamine agonist) or risperidone or haloperidol, may be more reasonable choices than adding another multi-receptor antagonist, but we emphasize that this theory based on receptor binding is very weak. Another pragmatic aim should be to avoid additive side effects in particular weight gain, orthostatic hypotension and anticholinergic load.

However, although we do not recommend antipsychotic combination treatments and these are generally associated with the risk for increased adverse effects, some isolated combinations have been associated with specific reductions in adverse effects in open label as well as randomized controlled trials (Gallego et al., 2012). This includes the reduction of hyperprolactinemia and amenorrhea when adding aripiprazole to haloperidol or risperidone and the reduction of body weight, lipid and glucose levels when adding aripiprazole to clozapine or olanzapine (but not when adding it to quetiapine of risperidone),

8. **Combinations of antipsychotics with other drugs: There is no evidence that would strongly support the use of any adjunctive agent for refractory positive symptoms (C). Adjunctive agents might be used for their target symptoms (e.g. benzodiazepines for sedation and anxiety, anti-manic drugs for manic symptoms, at best, knowing that even the evidence for such indications is extremely limited (C).**

Numerous augmentation strategies that have been examined to improve the positive symptoms of schizophrenia, but there was no clear effect of benzodiazepines (apart from sedation, (Dold et al., 2012)), beta-blockers (Cheine et al., 2003), lithium (Leucht et al., 2007b), carbamazepine (Leucht et al., 2007c) and valproate (Basan and Leucht, 2004). The largest valproate study (249 participants) showed a more rapid onset of improvement in the augmentation group at two weeks (Citrome et al., 2004), but even this effect was not replicated in another trial with 402 participants (Casey et al., 2009). Lamotrigine is a promising adjunct, but the results on each efficacy outcome in a Cochrane review were only based on two studies (Premkumar and Pick, 2006), and lamotrigine's superiority in meta-analyses restricted to clozapine non-responders was driven by an outlier (Sommer et al., 2011; Tiihonen et al., 2009, also see below). Moreover, the latter meta-analyses were relatively small and possibly not robust (Trikalinos et al., 2004). The effects of other augmentation strategies, such as polyunsaturated fatty acids (Omega-3 and Omega-6 fatty

acids (Joy et al., 2006), glutamatergic agents (Tuominen et al., 2006), estrogens (Chua et al., 2005), dehydroepiandrosteron (DHEA) (Elias and Kumar, 2007), amphetamines (Nolte et al., 2004), cyclooxygenase-2(COX-2) inhibitors such as celecoxib (Akhondzadeh et al., 2007) and erythropoietin (Ehrenreich et al., 2007) are either still in the experimental stage or inconclusive. In their meta-analysis of five trials Sommer et al., 2012 found a significant effect of adding non-steroidal anti-inflammatory drugs to antipsychotics, but they could not include a large unpublished trial that contained more patients than all 5 included studies together that showed no significant effects (Rappard and Müller, 2004). Therefore, adjunctive agents might at best be used for their target symptoms, e.g. benzodiazepines for sedation or mood-stabilisers for severe manic symptoms, keeping in mind that the evidence is even more limited, because many studies did not even address these target symptoms.

Concerning more information on the effects of adjunctive agents on specific symptoms, such as depression, negative symptoms or cognitive dysfunction, see below.

9. When clozapine fails: consider lamotrigine or topiramate (C), combine with other antipsychotics (C), consider ECT (C)

Justification:
Evidence for efficacy of augmenting clozapine is currently scarce. In a systematic review that analysed each adjunct individually (for example all antipsychotics added to clozapine were analysed individually rather than as one group) only adding lamotrigine or topiramate was associated with higher efficacy than placebo, but both results were driven by single outlier studies (Sommer et al., 2011). A meta-analysis on adding another antipsychotic to clozapine in non-response that pooled all antipsychotics as one group found a small but statistically significant superiority of the combination strategy (Taylor et al., 2012), but it left it unclear which combination is beneficial. In another meta-analysis by Barbui et al., 2009, the same combination strategy was, however, only superior compared to clozapine monotherapy in open RCTs.

In choosing an antipsychotic that is added to clozapine, it might be considered that clozapine has a low affinity to dopamine receptors. Therefore drugs that are selective for dopamine receptors such as amisulpride or sulpiride, but also aripiprazole (mainly a partial dopamine agonist), risperidone or haloperidol are more reasonable choices than adding another multi-receptor antagonist. As the evidence for these strategies is scarce the avoidance of additive side effects is another important goal. In this context, randomized controlled data may warrant consideration showing that aripiprazole augmentation of clozapine was associated with significant reductions in body weight and fasting glucose and triglyceride levels, even when keeping the clozapine dose stable (Zhang et al., 2010).

10. ECT may be considered as a last resort (A)

The evidence of ECT in treatment resistant patients is very limited. Tharyan and Adams, 2005 found a significant superiority of adding ECT to antipsychotics which was based only on a single small trial. But as ECT has a different mechanism of action than antipsychotic drugs, it may be considered as a last resort if all other attempts have failed. Moreover, a recently published randomised, open trial showed a clear advantage of clozapine non-responders

who received ECT (Petrides et al., 2015). It is well possible that this trial changes the overall results of the Cochrane review once it has been updated.

11. **<u>If adding and antipsychotic or other adjunct was not effective, it should be tapered off (C)</u>**
    As summarized above, the evidence of all combination strategies is limited. If such a combination is still tried, the response should be assessed and if it was ineffective it should be stopped to avoid side-effects, drug-drug-interactions and unnecessary cost.

B) Specific patient populations/symptoms

1. **Sedation of acutely agitated patients: Liquid formulations and rapidly dissolving tablets are useful to safeguard drug intake (C). Parenteral administration is often only needed in emergency situations when oral medications are not feasible (C). A well studied intervention is i.m. haloperidol combined with i.m. promethazine (A). Combining i.m. haloperidol with i.m. lorazepam or i.m. promethazine is more effective than haloperidol alone (A). Newer antipsychotics have advantages in terms of extrapyramidal side-effects (A). Overall, many options are available without clear superiority of one in all situations. In emergency situations, pragmatic issues (availability, ease of administration) as well as familiarity are critical considerations, and clinicians may wish to develop local protocols based on the evidence above that is most relevant to their situations (C)**

   Justification:

   There are many strategies for the treatment of agitated patients, such as monotherapy with an antipsychotic (high or low-potency, oral or parenteral , i.e., short-acting injectable or intravenous), monotherapy with a benzodiazepine, combining both, adding a sedating low-potency FGA, rapidly dissolving tablets, liquid and inhalable formulations etc. Liquid and rapidly dissolving tablets are options for safeguarding drug intake. Parenteral administrations are not more efficacious per se although they may have a more rapid onset of action, and are usually only necessary in emergency situations when patients refuse medication. The combination of haloperidol and lorazepam/promethazine seems to be more efficacious than monotherapy (Alexander et al., 2004; Battaglia et al., 1997; Huf et al., 2007). The newer antipsychotics aripiprazole, olanzapine and ziprasidone are available as intramuscular formulations (Citrome, 2007a). Their advantage includes fewer EPS than haloperidol. A general problem is that the studies on these newer agents were conducted for registration and all participants had to give informed-consent. These are not the patients for whom short-acting intramuscular medication is indicated (often violent patients who are not willing to take medication). From a methodological perspective, four large (200-300 participants), real-world, pragmatic trials with intramuscular medications need to be highlighted (Alexander et al., 2004; Huf et al., 2007; Huf et al., 2003; Raveendran et al., 2007). In these, the combination of haloperidol and promethazine produced more rapid tranquillization with fewer dystonic reactions than haloperidol alone (Huf et al., 2007) and no more EPS than lorazepam alone (Alexander et al., 2004). It did beat olanzapine in secondary outcomes (number of additional injections) with no difference in EPS, probably due to the anticholinergic properties of promethazine (Raveendran et al., 2007). Only intramuscular midazolam, a highly sedating benzodiazepine was more efficacious than haloperidol plus promethazine (Huf et al., 2003), but the mean dose of haloperidol in this study was lower compared to the other listed trials and so a dosing-effect leading to the favorable outcome for the benzodiazepine compound cannot be completely ruled out. In summary, a definite recommendation of a single strategy is not possible. In emergency situations, pragmatic criteria (availability, ease of administration) as well as familiarity are critical considerations

and clinicians may wish to develop local protocols based on the evidence above that are most relevant to their situations.

2. **Predominant persistent negative symptoms: Antipsychotics reduce general negative symptoms, but the evidence for negative symptoms that persist after acute treatment is limited (A). Rule out secondary negative symptoms due to extrapyramidal side-effects (e.g., by lowering the dose, a trial of anticholinergic medication, or switching to an antipsychotic with a low EPS risk) (C). Avoid secondary negative symptoms by using a drug with a low EPS risk (C). Low-dose amisulpride (50-300mg/day) is the best studied drug for this indication and is the only one that has been shown to be more efficacious than placebo in several trials (A). Adding an antidepressant can be effective (A-).**

   Justification:
   "General negative symptoms": Many acutely ill patients with schizophrenia present with both positive and negative symptoms. In such patients, all antipsychotics that have been evaluated have been shown to improve negative symptoms more than placebo and some new generation drugs (amisulpride, clozapine, olanzapine, risperidone) have been found to be more effective than older antipsychotics (mostly haloperidol and chlorpromazine) (Leucht et al., 2009a).
   Almost all relevant studies were conducted in patients suffering predominantly from positive symptoms and the doses of haloperidol were higher than those now recommended. In such patients, it is unclear whether the small advantage for negative symptoms related to primary negative symptoms or only to secondary negative symptoms, which can stem from positive symptoms, depression or extrapyramidal side-effects. Secondary negative symptoms due to EPS may be ruled out by lowering the antipsychotic dose, switching to an antipsychotic with a lower EPS risk or by a trial with anticholinergic medication. Therefore, such negative symptoms may resolve by the application of an antipsychotic alone and we would not recommend starting with a combination strategy.

   "Predominant persistent negative symptoms": Once the acute phase with positive symptoms has resolved, patients often present with persistent negative symptoms.

   Only studies in patients with primary/predominant negative symptoms, whose positive symptoms are low and remain stable, can clarify whether a medication is effective for this indication. Another major problem is that negative symptoms and symptoms of depression overlap and are difficult to disentangle by rating scales, and that several antipsychotic drugs also have antidepressant effects (Komossa et al. 2009). Nevertheless, the best evidence is for low-dose amisulpride (50-300mg/day) which proved superior compared to placebo in several trials (Leucht et al., 2002), but even this finding is complicated by a single trial in which only olanzapine 5mg/day, but not amisulpride 150mg/day or olanzapine 20mg/day were more effective then placebo. Only a few RCTs comparing antipsychotic drugs head-to-head in predominant negative symptoms are available (Leucht et al., 2009c), and among these only a single small trial showed a superiority of olanzapine compared to haloperidol (Lindenmayer et al., 2007). Several meta-analyses showed that adding an antidepressant may be effective for predominant negative symptoms (Rummel et al., 2006) or in patients with chronic schizophrenia (Sepehry et al., 2007; Smith et al., 2001), or in any patients with schizophrenia

and negative symptoms (Singh et al. BJP 2010). Again, to disentangle symptoms of depression and negative symptoms may have been difficult. For example, For example, in one trial, exclusion of depressed patients led to disappearance of the previously noted significant improvement in negative symptoms with adjunctive antidepressant use (Saha et al., 2007).

3. **Depressive symptoms: Depressive symptoms associated with an acute episode of schizophrenia should not be automatically treated with an antidepressant, because they may resolve with the treatment with an antipsychotic alone (A). If there is a suspicion of antipsychotic induced depressive symptoms, these should be ruled out by dose reduction, anticholinergic medication or by switching to a drug with a lower EPS risk (C). Persistent or post-psychotic depression may be treated with an antidepressant added to the antipsychotic (A). The risk to provoke an exacerbation by adding an antidepressant is low (A-).**

   Justification:

   Depressive symptoms are frequently present in acutely ill patients with schizophrenia (Hausmann and Fleischhacker, 2002). Because they are associated with positive symptoms and may thus improve with antipsychotics alone (Leucht et al., 2009a), we would not recommend adding an antidepressant immediately. Moreover, in a meta-analysis some newer antipsychotic drugs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine) had superior antidepressant properties compared to older drugs (mainly haloperidol and chlorpromazine) in people with schizophrenia (Leucht et al., 2009b). Some newer antipsychotics have also obtained an officially approved indication for major depressive disorder in some countries (e.g. quetiapine in the EU and the US, aripiprazole in the US; or amisulpride for dysthymia in Italy). Moreover, older literature suggested that drugs which produce a lot of EPS (in particular first generation antipsychotics, such as haloperidol or fluphenazine) may produce “akinetic depression” (Van Putten, 1978), i.e., depression-like symptoms. We would therefore recommend switching to a drug with low EPS risk in such occasions.

   Studies that demonstrated the effectiveness of antidepressants for depression systematically excluded people diagnosed with schizophrenia. While it is reasonable to assume that depressive symptoms in the context of schizophrenia might also improve with antidepressant treatment, scant evidence supports this. A Cochrane review found some evidence that antidepressants are effective for post-psychotic depression, but the number of trials was small and most (but not all) used tricyclic antidepressants, which are currently not first choice (Whitehead et al., 2003). The risk that an adjunctive antidepressant may provoke psychosis has been judged to be small (Siris, 1993; Whitehead et al., 2003).

4. **Manic symptoms: Manic symptoms associated with an acute episode should not be automatically treated with an anti-manic treatment because they may resolve by treatment with an antipsychotic alone (C). If manic symptoms persist, the addition of an anti-manic drug, such as lithium, valproate or carbamazepine, may be tried (C).**

   Justification:

   It should be noted that the recommendation and the following text refers to manic

symptoms associated with schizophrenia, and not to schizoaffective disorder where different rules may apply. Manic symptoms can be present in patients with schizophrenia. They may often remit when treated with an antipsychotic alone, because many antipsychotics have been shown to be effective for bipolar mania (Cipriani et al., 2011). We would therefore not generally recommend combining an antipsychotic with an anti-manic drug in the presence of manic symptoms. However, if manic symptoms cannot be controlled with an antipsychotic alone, the addition of lithium, valproate or carbamazepine may be warranted, although meta-analyses have not found a superiority of adding these drugs to antipsychotics for manic symptoms. These meta-analyses were, however, limited by the fact that most of the included studies focused on positive symptoms so that very few data on manic symptoms were available (Basan and Leucht, 2004; Leucht et al., 2007b; Leucht et al., 2007c). Single randomized trials showed that adding carbamazepine (Klein et al., 1984), valproate (Casey et al., 2003) (not replicable in a later study (Casey et al., 2009) or lithium (Biederman et al., 1979) to antipsychotics reduces mania/"excitement" associated with schizophrenia.

5. **Obsessive-compulsive symptoms: if such phenomena are symptoms of the psychosis, the antipsychotic treatment must be optimized (C). An SSRI might be helpful (C). If obsessive-compulsive symptoms are thought to be side-effects of the antipsychotic drug, switching the antipsychotic is an option (C).**

   Justification: The dilemma is that obsessive compulsive symptoms can be part of the schizophrenia symptomatology. But there are also case reports suggesting that obsessive-compulsive symptoms are side-effects of antipsychotic drugs (Scheltema Beduin et al., 2012; Schirmbeck and Zink, 2012) . This makes theoretical sense, as many of the newer antipsychotics have the opposite mechanism of action as SSRIs in that they block serotonergic receptors (Kim et al., 2012). Many of these case reports were on clozapine or risperidone, but this does not necessarily mean that the phenomenon is limited to these drugs (Scheltema Beduin et al., 2012). To disentangle both factors can be clinically very difficult and often impossible. One criterion is whether the obsessive compulsive symptoms were present before antipsychotic treatment or whether they started only afterwards. The guideline group is not aware of RCTs for patients with both schizophrenia and obsessive compulsive symptoms. Pragmatically, if obsessive compulsive symptoms are part of the psychosis, the antipsychotic treatment must be optimized. An SSRI might also be tried, but should be stopped if ineffective. If obsessive compulsive symptoms are thought to be side-effects of the antipsychotic drug, switching the antipsychotic, perhaps to one without a prominent serotonergic blockade, may be considered.

6. **Anxiety: short-term addition of a benzodiazepine can be useful (A-).**

   Justification: A systematic review found no convincing evidence for benzodiazepines in schizophrenia apart from rapid tranquillisation of acutely agitated patients (Dold et al., 2012)). A few old RCTs (Azima et al., 1962; Gundlach et al., 1966; Minervini et al., 1990; Morphy, 1986) included in this Cochrane review examined the effects of benzodiazepines in people with schizophrenia and anxiety, and some mentioned positive effects. These studies were, however, typically small and often so poorly reported that they could not be used for meta-analytic calculations. The guideline group, nevertheless, felt that due to the well-

documented anxiolytic effects of benzodiazepines in non-psychotic patients, adding a benzodiazepine to treat anxiety symptoms may be useful. Similar logic suggests that a SSRI might be tried, but the group is not aware of any RCT on this strategy and would also not generally recommend their use in this indication based on the personal experiences of the guideline group.

7. **Insomnia: Attempt first non-pharmacological approaches, such as sleep-hygiene advice (C); if insufficient alone, apply together with pharmacologic options (C). Antipsychotic drugs with a sedating profile can be useful (C). If this is not sufficient, benzodiazepines/non-benzodiazepine hypnotics, sedating antipsychotics or sedating antidepressants can be added (C).**

   Justification: Certain antipsychotics are more sedating than others (see Table 1 and (Leucht et al., 2013a)). Such a sedating property can be useful in patients suffering from insomnia, although we are not aware of RCTs in patients with schizophrenia selected for insomnia, which would be the rigorous test of this approach. We are also not aware of comparative randomized controlled trials on other options for patients with schizophrenia and insomnia, such as adding benzodiazepines/non-benzodiazepine hypnotics or sedating antidepressants, or adding to switching to sedating antipsychotics. Such drugs should be chosen according to their side-effect profiles, risk for drug-drug interactions with the antipsychotic, and potential for abuse. Furthermore, as in other patients, sedative-hypnotics should be tried after, and in concert with, non-pharmacological approaches and sleep-hygiene advice.

8. **Cognitive dysfunction: Antipsychotics improve cognitive function compared to placebo but the benefits are small (A). There is little evidence to guide the choice of antipsychotics for this indication. Acetylcholinesterase inhibitors and memantine have generally not been shown to be efficacious (A).**

   Justification: In contrast to a long-held opinion that first-generation antipsychotic drugs worsen cognitive function, a meta-analysis found a small, but statistically significant improvement of such antipsychotics compared to placebo (Mishara and Goldberg, 2004). Advantages of any specific antipsychotic are not very clear. A meta-analysis found that, as a group, clozapine, olanzapine, quetiapine and risperidone improved cognitive function modestly more than haloperidol (Woodward et al., 2005). However, in CATIE, perphenazine was at least as effective as olanzapine, quetiapine, risperidone and ziprasidone for cognition (Keefe et al., 2007), and in EUFEST there was no difference between low-dose haloperidol and amisulpride, olanzapine, quetiapine and ziprasidone (Davidson et al., 2009). There is no evidence that antipsychotics improve cognitive deficits outside of the context of treating people with psychotic illnesses.

   Trials of acetylcholinesterase inhibitors to improve cognitive deficits mostly have not proven to be effective (Stip et al., 2007) although a study with galantamine showed improvement on select neuropsychological functions compared to placebo (Buchanan et al., 2008). There is no convincing randomized evidence on memantine for cognition in schizophrenia. Although one of two very small trials (less than 30 participants showed a superiority of memantine compared to placebo added to antipsychotics (de Lucena et al., 2009), the other one found no difference (Lee et al., 2012), and the largest RCT was negative (Lieberman et al., 2009).

9. **Chronic aggressive behavior: Address the root of aggression. For example, if aggression is associated with positive symptoms, optimized treatment of symptoms and drug adherence are key (C). Clozapine was the most effective drug in an appropriate trial in chronically aggressive patients (A). The evidence for other newer antipsychotics or anti-manic drugs, such as lithium, carbamazepine or valproate, is methodologically less convincing (C).**
Justification: Citrome (Citrome, 2007b, c) stressed the importance of considering the root of aggression. If it is due to positive symptoms, optimized treatment of psychopathology and adherence are key (for the role of depot treatment see maintenance treatment below). If aggression is caused by drug or alcohol abuse, or by social problems, these need to be addressed. In terms of pharmacological interventions, the guideline group is only aware of one antipsychotic drug trial that was conducted in patients specifically selected for chronic aggressive behavior. In this study, clozapine was more effective than haloperidol and olanzapine to reduce aggression, and this effect was independent of improvements in psychopathology (Krakowski et al., 2006). The evidence for other (newer) antipsychotic drugs is less strong, because it was derived from post-hoc analyses of RCTs that were conducted in patients who were not necessarily aggressive. In EUFEST olanzapine had an advantage over haloperidol, amisulpride, quetiapine and ziprasidone in managing hostility (Volavka et al., 2011). Therefore, it was difficult to disentangle antiaggressive effects from effects on other symptoms, limiting generalizability . The same problem holds true for lithium and antiepileptic drugs, for which the evidence in schizophrenia is scant (Citrome, 2007b, d; Citrome et al., 2007)). The recommendation for other treatments, such as beta-blockers or SSRIs, was even more cautious (Citrome, 2007a, b).

10. **Suicidality: clozapine has been shown to be efficacious in such patients (A)**

Justification: The guideline group is only aware of one large randomized controlled trial in people with schizophrenia selected for suicidality. Clozapine was more effective than olanzapine in this study (Meltzer et al., 2003). In a post hoc analysis sertindole reduced suicidal attempts to a greater extent than risperidone (Crocq et al., 2010).

11. **Dual diagnosis: Antipsychotics are appropriate treatments for schizophrenia when there is a co-occurring substance use disorder, being likely effective for schizophrenia symptoms (A-). There is no strong evidence to support the preferential use of any antipsychotic (C). A long-acting injectable antipsychotic may be helpful in this situation to improve medication adherence (C). Antipsychotics do not seem to exert an effect on primary alcohol or cocaine/psychostimulant dependence (A).**

Justification: Few RCTs in dual diagnosis patients showed significant improvement in schizophrenia symptoms and mixed/unclear results for substance use (Akerele and Levin, 2007; Rubio et al., 2006; Sayers et al., 2005). However, studies were generally small and compared two antipsychotics head-to-head (without clear group differences) and lacked a placebo group, so that the effect of time cannot be ruled out. Of note, in two recent meta-analyses, there was no beneficial effect of antipsychotics for primary substance abuse in alcohol dependent (Kishi et al., 2013) and cocaine dependent substance abusers without schizophrenia (Amato et al., 2007). Approved medications for substance dependence can be tried, but evidence of benefit is scarce. One RCT showed that naltrexone and disulfiram are

more effective than placebo in promoting abstinence from alcohol in people with psychotic disorders (Petrakis et al., 2006). There is no evidence from RCTs supporting the use of acamprosate for people with schizophrenia. Psychosocial substance abuse treatments should be offered in addition to pharmacologic interventions (Dixon et al. PORT recommendations (Dixon et al., 2010)).

12. **Adolescents: Antipsychotic drugs are efficacious in children and adolescents with schizophrenia (A). Drug tolerability should guide the choice of antipsychotic (A). Clozapine has shown to be a more efficacious antipsychotic in adolescents with treatment resistant schizophrenia (A).**

    Justification: Based on successful, 6-week, placebo controlled trials, newer antipsychotics, such as aripiprazole, olanzapine, paliperidone, quetiapine and risperidone, have FDA indication for schizophrenia in patients ages 13-17, and in this age group only ziprasidone failed to separate from placebo (Schimmelmann et al., 2013). The few head to head comparisons have not shown differences in terms of different efficacy between antipsychotics in this age range (Arango et al., 2009; Kumra et al., 1996; McClellan et al., 2007; Sikich, 2008; Sikich et al., 2008), with the exception of more efficacy for clozapine in adolescents with treatment refractory schizophrenia (Kumra et al., 2008). Although no direct comparison with the adult population has been conducted, a number of side effects are more frequent in adolescents compared to adults. These include sedation, EPS, withdrawal dyskinesia, prolactin elevation, weight gain and lipid abnormalities (Correll et al., 2006). In addition, the developing brain and body may have more long lasting effects from drug side effects. In adolescents, side effects profile vary widely between different antipsychotics (Correll et al., 2009a; Fraguas et al., 2011). For instance, the numbers-needed-to-harm for weight gain ≥7% went from 39 (confidence interval [CI]: -1 to +6, not significant) with aripiprazole to 3 (CI: 3-4) for olanzapine (De Hert et al., 2011c). Based on the metabolic side effect profile, there is no rationale for using olanzapine as first line treatment in adolescents. Metabolic adverse events should be monitored with all antipsychotics early during treatment, as in adolescents and in never treated or first episode patients, cardiometabolic effects are most pronounced (Correll et al., 2009a).

13. **First episode patients: Overall they respond better to antipsychotic drugs than chronic patients and seem to need lower doses (B) which could be targeted at the lower end of officially registered ranges (C). Side-effects may therefore play an even higher role in choosing among antipsychotic drugs than in more chronic patients (C), although some evidence suggests in part similar efficacy differences between drugs as in chronic populations (A).**

    Justification: Although the guideline group is not aware of a systematic review that compared drug efficacy in first-episode patients with more chronic patients, there are many examples in the literature suggesting that the former respond better to drugs. For example, in a pivotal study comparing risperidone with haloperidol in “general” schizophrenia patients, 63% responded to the best risperidone dose, but response was based on only at least 20% PANSS reduction from baseline (Peuskens and Group., 1995). In a first-episode study comparing risperidone and haloperidol, again 63% responded, but the response

threshold was much higher (at least 50% PANSS reduction, (Emsley and Group, 1999)). Furthermore, in the large effectiveness study CATIE, overall, 11.7% of chronic patients achieved remission as defined by (Andreasen et al., 2005), (Levine et al., 2011), compared to 30% of first-episode patients in the effectiveness study EUFEST (Boter et al., 2009). In (Robinson et al., 1999b) and (Lieberman et al., 2003), more than 80% of first-episode patients achieved a remission of positive symptoms (different criteria than those by (Andreasen et al., 2005)) within one year. Supported by the fact that large scale pragmatic trials have shown clear advantages of new generation antipsychotics over even a low dose of haloperidol (eg. EUFEST; Kahn et al., 2008) especially also with respect to motor side effects (Rybakowski et al., 2014), the guideline group recommends that side-effect profiles should play an even greater role in drug choice for first-episode patients. While Crossley et al. 2010 found no difference between the groups of first-generation and second-generation antipsychotic drugs (Crossley et al., 2010), a more comprehensive meta-analysis only replicated the lack of differences between these two drug groups for total psychopathology and positive symptoms (Zhang et al., 2012). By contrast, second-generation antipsychotics were significantly better for negative symptoms, cognition and relapse prevention (small effect size) and were associated with significantly lower all-cause discontinuation rates and discontinuation due to inefficacy and intolerability (25-40% risk reduction), findings that seemed independent of haloperidol comparator doses (Zhang et al., 2012). However, the first-generation comparator was almost exclusively haloperidol and we feel that this broad classification is not valid because both first- and second-generation antipsychotics are heterogeneous groups (Leucht et al., 2013a). While the average doses in first-episode studies with flexible dosing were often relatively low (e.g. (Emsley and Group, 1999)), there are no evidence-based estimates. However, we would suggest to target doses at the lower end of the officially registered dose ranges.

14. **Elderly patients with schizophrenia: the same principles apply, but this group is more sensitive to side-effects of antipsychotic drugs (B) and the target doses should be lower than for younger adult patients (C).**

Justification: Due to various factors, such as decreased drug metabolism, lower plasma protein concentrations, elderly patients are more sensitive to antipsychotic side-effects. For example, the risk for tardive dyskinesia in elderly patients has been repeatedly documented to be considerably higher than in younger adults (Caligiuri et al., 2000). Therefore, side-effects play an even more important role for drug choice in this population. Similarly to first-episode patients, doses at the lower end of officially registered dose ranges are often sufficient and better tolerated.

C) RELAPSE PREVENTION WITH ANTIPSYCHOTIC DRUGS

1. Indication: Maintenance treatment with antipsychotic drugs is effective (A) and indicated for all patients, except for those in whom side-effects outweigh the benefits, those with very mild episodes and unclear diagnoses (C).

1. Justification: In a recent review, maintenance treatment with antipsychotic drugs clearly reduced relapse rates from 64% to 27% within 11 months (Leucht et al., 2012). In naturalistic studies, approximately only 20% of patients with a first episode did not experience another episode within 5 years (Robinson et al., 1999b; Shepherd et al., 1989). As there are no valid indicators that could predict which patients will not relapse, we follow the recommendations of an early guideline that suggested continuous maintenance treatment with antipsychotic drugs for all patients, except for those in whom side-effects outweigh the benefits, those with very mild episodes and unclear diagnoses (Kissling et al., 1991).

2. Maintenance treatment should be given continuously rather than using an intermittent approach (A). The latter may be used combined with monitoring of early warning signs for those patients who do not accept continuous treatment (A-)

Justification: Intermittent treatment (tapering medication once a patient is in remission and only re-starting it when there are early warning signs such as problems in concentration or sleep, or attenuated positive symptoms) was less efficacious than continuous treatment (Carpenter et al., 1990; Herz et al., 1991; Jolley and Hirsch, 1990; Pietzcker et al., 1993; Schooler et al., 1997), even in first-episode patients (Gaebel et al., 2011; Wunderink et al., 2007). However, in Wunderink et al., 2007 gradual discontinuation was associated with higher relapse rates, but not with differences in functional outcomes. Moreover, in one of these studies, intermittent treatment started in case of early warning signs was superior to waiting for a full relapse (Pietzcker et al., 1993). Therefore, in patients who do not accept continuous treatment, intermittent treatment can be an option.

3. Maintenance treatment can be carried out with the antipsychotic drug that was effective and well tolerated in the acute phase (A). However, the higher risk of haloperidol for tardive dyskinesia and the weight gain risk of many antipsychotics should be considered (A).

Justification: A systematic review (Kishimoto et al., 2013a) found few differences between single second-generation and first-generation antipsychotics in terms of relapse prevention. As a group, second-generation antipsychotics were superior (relapse rates: 29% vs 37.5%), but the classification into first- and second generation is questionable (Leucht et al., 2009b; Lieberman et al., 2005) and almost all studies used haloperidol as a comparator. A clearer advantage includes less tardive dyskinesia, which occurred with an annual incidence of 3.0% in second-generation antipsychotics versus 7.7% with first-generation antipsychotics (again mostly haloperidol, Correll and Schenk, 2008). Many second-generation antipsychotics and low-potency first-generation antipsychotics are associated with weight gain and associated metabolic problems (Allison et al.,

1999), but in contrast to tardive dyskinesia weight gain usually starts early after initiation of treatment and can therefore already be detected in the acute phase.

4. Depot formulations is an option for many patients (B)

Justification: Non-compliance is very frequent and difficult to detect in schizophrenia. Major advantages of depot drugs are that medication intake is assured and that the doctor immediately knows when patients stop their treatment. However, a large systematic review of randomized controlled trials by Kishimoto et al., 2012 found no difference between the groups of depot and oral antipsychotics for relapse prevention. According to the criteria of this guideline, depot drugs can therefore not be generally recommended for people with schizophrenia. However, the authors also highlighted the major limitation of their meta-analysis. Depot formulations are not more efficacious per se, but they could have advantages in terms of better monitored compliance. In addition, patients who consent to a randomized (and often blinded) trial may be more compliant than patients in everyday clinical care and receive more attention, reminders, etc, thereby, limiting the potential to demonstrate any superiority of depot antipsychotics (Rauch and Fleischhacker, 2013). Indeed, in epidemiological (Tiihonen et al., 2011; Tiihonen et al., 2006) and mirror image studies (Kishimoto et al., 2013b; Davis et al., 1994) in which patients were studied who received depot antipsychotics as part of clinical care, depot drugs were superior to oral antipsychotics. Moreover, depots were never *less* efficacious than oral forms of administration in the RCTs. Therefore, depot should at least be offered to people who accept this formulation, but should always be considered when non-compliance is a problem.

3. **Dosage in relapse prevention: We recommend keeping the dose that was effective in the acute phase as long as there are no important side-effects (A-).**

Justification:

It is unclear whether lower doses than usually applied in the acute phase are sufficient for maintenance treatment. In an early meta-analysis, higher dosages of conventional antipsychotics than 375 mg/day chlorpromazine equivalent did not produce additional effectiveness in maintenance therapy (Bollini, 1994). In another systematic review, dosages between 50-100mg/day chlorpromazine equivalent led to more relapses than doses between 200 and 500 chlorpromazine equivalents (Barbui et al., 1996). In the most recent systematic review, standard antipsychotic doses (e.g. quetiapine ≥ 400mg/day or olanzapine ≥ 10mg/day) were consistently more effective than 'very low' doses (e.g. quetiapine <200mg/day or olanzapine <5mg/day), while the comparisons of relapses with 'low' doses (e.g. quetiapine 200-400mg/day or olanzapine 5-10mg/day) was only of borderline statistical significance (Uchida et al., 2009). The authors, however, discussed the limited database. In the study most directly addressing the question of lowering the antipsychotic dose (which was published after the meta-analysis by Uchida et al. 2009), maintaining the risperidone dose that was effective in the acute phase was significantly more effective in reducing relapse compared to 50% dose reductions after either 4 weeks or 6 months of acute-phase dosing (Wang et al., 2010). In a further RCT published after the meta-analysis by Uchida et al. 2009, low dose olanzapine depot (150mg biweekly, thought to approximately correspond to 10mg/day oral), was associated with significantly more exacerbations than 300mg/biweekly (thought to approximately correspond to oral olanzapine 20mg/day (Kane et al. 2010). The guideline group felt that, overall, the situation

is not clear, as small dose reductions by for example 10% or 25% etc were not systematically assessed. We pragmatically recommended to keep the dose that was effective in the acute phase as long as it was well tolerated.

4. Excessive doses (C), antipsychotic polypharmacy (A-) and non-antipsychotic polypharmacy which may have accumulated in the acute phase should be carefully reduced (C)

Justification:

Although the evidence supporting both doses considerably above the officially licensed dose ranges and polypharmacy is very limited (see above), these practices are still encountered frequently. The maintenance phase may be used to reduce excessive dosing and polypharmacy. In a recent trial, stopping one of two antipsychotics was followed by more frequent treatment discontinuation than when both antipsychotics were continued (absolute difference 26%, Essock et al., 2011). However, it was possible to successfully switch two-thirds of participants to monotherapy, and the groups did not differ with respect to necessity of hospitalization or symptoms. Moreover, monotherapy resulted in significant weight loss. These results support attempts to reduce polypharmacy and the reasonableness of prescribing guidelines encouraging trials of antipsychotic monotherapy for individuals receiving antipsychotic polypharmacy, as long as patients are allowed to restart polypharmacy if antipsychotic monotherapy does not work.

5. Any dose reduction should be performed very slowly to avoid withdrawal effects (A-) and rebound psychoses (C).

Justification:

There is a theory that long-term use of antipsychotic drugs increases dopamine receptor sensitivity. If antipsychotics are withdrawn abruptly rather than gradually, this could then lead to withdrawal effects and rebound psychoses ("supersensitivity psychosis", Chouinard and Jones, 1980; Moncrieff, 2006)). Indeed, in a meta-analysis there was significantly more dyskinesia in the withdrawal group than in the antipsychotic continuation group (Leucht et al., 2012), and various withdrawal effects, such as agitation, anxiety and insomnia, which are thought to be related to hypersensitivity of histamine or cholinergic receptors after prolonged blockade with some agents, are well known clinical phenomena (Correll, 2010). However, the same meta-analysis (Leucht et al., 2012) did not find a difference in relapse risk between the subgroups of studies that withdrew antipsychotics abruptly or gradually. In the same meta-analysis, even when excluding participants who had relapsed within the first nine months of the studies and thus only examinining "9-month survivers", significantly more patients in the placebo groups relapsed. This finding can be used as an argument against rebound psychosis, because such effects should occur early after stopping medication and not after 9 months. Nevertheless, meta-analyses may not be sensitive enough to detect such effects, and there are animal data supporting the possibility of supersensitivity psychosis, at least in vulnerable subgroups of patients (Leucht et al., 2013b; Samaha et al., 2007; Silvestri et al., 2000). We therefore strongly recommend to reduce doses slowly, e.g. by not more than 10%-20% per month.

6. Duration of antipsychotic relapse prevention: at least 6 years for multiple episode patients and at least 1 year for first-episode patients (A-). The severity of episodes, current

psychopathology, suicidal acts or aggression during acute episodes should also be considered (C).

Justification:
The question is whether patients who have been symptomatically stable or even in remission for a given number of years still need maintenance treatment or whether they are "cured" and do not need it any longer.
Multiple episode patients: In a meta-regression Leucht et al., 2012 found no association between the duration participants had been stable before entering a trial and the reduction of relapse risk by antipsychotics compared to placebo. Thus, there is no evidence that the longer patients have been stable the less would they be in need of medication. In single studies withdrawing antipsychotics led to more frequent relapses than continuing them even in those patients who had been stable for at least 3-5 years (Cheung, 1981) and 6 years (Sampath et al., 1992), but both studies together comprised only 54 participants. We, therefore, tentatively recommend 6 years as a minimum duration for maintenance treatment of multiple-episode patients, because data in patients who have been stable for more than 6 years are not available. But 54 participants obviously represent a very small database and more trials are needed.

First episode patients: It should be noted that in a meta-analysis there was no difference in reduction of relapse risk by antipsychotics between first-episode and multiple-episode populations. This means that first-episode patients generally benefit as much from maintenance treatment as multiple-episode patients (Leucht et al. 2012). This is also underscored by more recent reviews by Zipursky et al., 2014 and Emsley and Fleischhacker, 2013 who reported relapse rates of up to 90 % in patients discontinuing antipsychotics. However, if the longest duration patients had been stable before entering a relapse prevention study is used as a criterion, this duration was one year (Chen et al., 2010), because there are no maintenance studies in first-episode patients who had been stable for longer than one year. We emphasize that one year is a minimum recommendation. It in part also does justice to the phenomenon that approximately 15%-20% of first-episode patients may not have a second episode, at least in the first 5 years of treatment, and will therefore receive unnecessary treatment (Robinson et al., 1999a; Shepherd et al., 1989). Unfortunately there are no valid predictors to identify these patients. Therefore, we follow previous recommendations that all patients should be treated (Kissling et al., 1991). A randomized controlled trial from the Netherlands, originally reporting higher relapse rates in patients following a guided discontinuation strategy (Wunderink et al 2007), found, in a *post hoc* analysis of longer-term outcomes after the controlled trial period, better recovery rates among those originally assigned to the discontinuation strategy (Wunderink et al., 2013). While this result confirms that some first-episode patients do well without long-term antipsychotics, the evidence is not equivalent to that from a randomized controlled trial designed to address the question because post-randomization selection factors very likely influenced the result.

For both subgroups we recommend that the severity of prior episodes as well as suicidal acts or aggression during acute episodes should be taken into account when considering the minimum duration of antipsychotic relapse prevention (Kissling et al., 1991). Another criterion is the current level of symptoms and functional status. If patients are just improved, but not in remission, we would be very hesitant to consider to withdraw medication.

D) PROPHYLAXIS/MANAGEMENT OF SIDE-EFFECTS

1. Extrapyramidal side-effects

a) Dystonia: This side-effect can be effectively treated with anticholinergics (e.g., biperiden or benztropin) (C). The effects of intravenous treatment are usually prompt. (C) Risks, especially of intraveneous administration, are exacerbation of schizophrenia and anticholinergic side-effects including delirium. Pragmatically, anticholinergic medication should be continued for some time after the dystonia or the antipsychotic drug can be changed to avoid a reoccurrence (C).

Justification: We are not aware of systematic reviews or randomized trials on the treatment of this side-effect, but there is no doubt about the effectiveness of anticholinergics. The risk for acute dystonia is highest for high-potency conventional antipsychotics such as haloperidol. Other risk factors are high dose and rapid dose increase, young men seem to be more frequently affected.

b) Parkinsonism (rigidity, tremor, akinesia): The therapy consists of anticholinergics (e.g., biperiden, benztropin) or dopamine agonists (e.g., amantadine), dose reduction or change of the antipsychotic drug (C). In case of antipsychotics with a high EPS risk, prophylactic anticholinergic medication should be considered (A).

Justification: We are not aware of a systematic review on the recommended treatment strategies. Prophylactic anticholinergic medication should be considered only for antipsychotics with a high EPS risk, because such medication has side-effects, as well. In 1991 Lavin and Rifkin produced a review on prophylactic anticholinergic medication (Lavin und Rifkin 1991a) and on the withdrawal of such medication (Lavin und Rifkin 1991b). While they found more than 30 RCTs for the latter question, only few studies had examined prophylactic administration right from the start. After careful consideration of the benefits and risk, they opted for prophylactic administration with high potency first-generation antipsychotics. If anticholinergics are used prophylactically, we recommend attempting to reduce and stop this medication after maintenance dose and therapy have been implemented. This is also in line with a WHO recommendation that cautious against using anticholinergics prophylactically (World Health Organisation, 2010).

c) Akathisia: Therapeutic options are ß-blockers (e.g. propranolol), benzodiazepines (e.g., lorazepam, clonazepam, diazepam) or anticholinergics (e.g. biperiden, benztropin), as well as mirtazapine but often the antipsychotic dose has to be reduced or the antipsychotic changed (C)

Justification: Although ß-blockers, benzodiazepines, anticholinergics and mirtazapine (Poyurovsky, 2010) are frequently recommended, Cochrane reviews found that the evidence for all four strategies is limited if any (Lima et al., 2004a; Lima et al., 2002; Lima

et al., 2004b). In a review, Miller and Fleischhacker, 2000 argue that the best available evidence points towards propranolol as the treatment of first choice. In practice, it will be frequently necessary to decrease the antipsychotic dose or to switch to another antipsychotic.

d) **Tardive dyskinesia: Switch the antipsychotic to a less EPS prone one (B), reduce the dose (C). Consider tetrabenazine (B). No pharmacologic intervention for TD has been found to be convincingly effective (A-).**

Justification: Soares und McGrath 1999 summarized the results of their Cochrane reviews on the treatment of tardive dyskinesia and found very small numbers of RCTs and participants for the various interventions (among others tiapride, tetrabenazine, vitamine E, vitamine B6, switching to clozapine and many others). In our opinion, none of them can be generally recommended. The randomized evidence for pragmatic solutions such as switching to a less EPS prone antipsychotic (especially clozapine) is also limited to open switch studies and case series, but it is the best recommendation we can make at this point. It is based on the assumption that those antipsychotics with a high risk for acute EPS are also associated with a higher risk for tardive dyskinesia. The American Academy of Neurology also suggests to consider tetrabenazine (Bhidayasiri et al., 2013).

e) **Neuroleptic malignant syndrome (NMS): Stop antipsychotic, refer to intensive care unit, hydration, treat with dopa-agonists (e.g. amantadine, bromocriptine) or muscle relaxants such as dantrolene, consider ECT (C).**

Justification: As the phenomenon is rare, the evidence is based only on case reports and case series. The problem is that it is difficult to entangle MNS from severe catatonia. In the case of doubt antipsychotics should be stopped. Benzodiazepines, dopaminergic agents such as bromocriptin, dantrolene as well as ECT have been described as helpful, usually in case reports or small case series (Strawn et al., 2007).

2. **Sedation: Wait to see whether sedation is transient (C). Use most of the dose in the evening (C). Reduce the dose (C). Switch to another, less sedating antipsychotic (A)**

Justification: Antipsychotic drugs differ in their sedating properties (Leucht et al., 2013b), therefore switching to a less sedating one is an obvious option. Low-potency first-generation antipsychotics, such as chlorpromazine, but also some second-generation antipsychotics, such as clozapine, zotepine, quetiapine or olanzapine, are more sedating than others. However, to change the antipsychotic is not always possible. As sedation can be transient, it can be worthwhile to wait for some time whether it remits spontaneously. Other pragmatic strategies are to reduce the dose or to give most of the dose before sleep to avoid plasma-level peaks during the day.

3. **Weight gain and associated metabolic side-effects (glucose and lipid abnormalities): Prevent by choosing an antipsychotic with little weight gain (A). Facilitate life-style changes, diet and physical exercise (A). Switch to a lower-risk antipsychotic (A). Try adding metformin or topiramate to reduce weight (A). Use antihypertensives, lipid lowering drugs (e.g., statins) and antidiabetic agents if indicated (A).**

Justification: Although various strategies to reduce overweight and related metabolic side-effects have been developed and for several ones positive evidence is available, questions about the magnitude of their effects, their long-term effectiveness and their side-effects remain. Therefore, prevention in terms of choosing an antipsychotic with a low weight gain risk plays a key role (Faulkner et al., 2007, see Table 1). Non-pharmacological strategies are not the focus of this guideline, but patients and their relatives should definitely be educated about and motivated for therapeutic life-style changes, including adequate physical activity and a healthy diet, as weight management interventions have shown significant benefits over control conditions (Caemmerer et al., 2012). One beneficial option with randomized controlled evidence is the switch to an antipsychotic with significantly lower weight gain potential (Stroup et al., 2011). Among the many drugs that have been tried to reduce weight as adjunctive treatments to antipsychotics in schizophrenia, the best evidence is currently available for metformin (Mizuno et al., 2014). Although we do not endorse antipsychotic polypharmacy (see above), for clozapine treated patients another option may be adding aripiprazole, which in an adequately powered RCT was associated with significantly more weight loss than adding placebo (Fleischhacker et al., 2010). Guidelines also emphasize that drugs like antihypertensives, lipid lowering drugs (e.g., statins) or antidiabetic agents should be used if indicated, because this is not sufficiently done in people with severe mental illness (De Hert et al., 2011a; de Hert et al., 2011b).

4. Cardiovascular side-effects

a) Orthostatic hypotension and reflex tachycardia: advise to stand up slowly, slow dose increase, dose reduction, divide into several doses per day, change the substance (C)

Justification: Orthostatic hypotension (drop of blood-pressure when standing up) and resulting compensatory reflex tachycardia are explained by alpha-1 receptor blockade of certain antipsychotics. The listed recommendations are of pragmatic nature.

b) Tachycardia: Dose reduction (C), change the antipsychotic (C), add a ß-blocker (C)

Justification: Tachycardia can also be the result of anticholinergic effects of antipsychotics (e.g., clozapine). In addition to pragmatic measures, the addition of a ß-blocker can be useful.

f) QTc prolongation, higher grade arrhythmias: reduce the dose (C), change the antipsychotic (A), monitor electrolytes, comorbidities and co-medication (C)

Justification: the treatment with antipsychotic drugs can also be associated with arrhythmias such as bundle branch blocks, changes of the QRS complex, etc, and, in the worst case, potentially fatal torsades de pointe. Prolongation of the QTc interval, which can predispose to arrhythmias, occurs with many antipsychotics, but few prolong the QTc to a significant degree (see Table 1). QTc intervals $\geq$500 msec are associated with a higher frequency of torsades de pointe and sudden death, and should therefore lead to switch to an antipsychotic with a lower QTc prolonging potential. QTc >450msec is usually considered to be potentially dangerous, but the association between QTc and arrhythmias at that level is less clear. Among first-generation antipsychotics, the risk for

QTc prolongation seems to be highest with thioridazine and pimozide; among second-generation antipsychotics sertindole, amisulpride and ziprasidone seem to be most affected (see Table 1, and Leucht et al., 2013b). Obviously, QTc prolonging drugs are especially problematic in patients with known heart disease, congenital long QT syndrome, a history of syncope and other risk factors. As the risk is often dose related, dose reduction may be tried, if possible. Electrolyte imbalances (e.g., hypokalemia or hypomagnesemia) can increase the risk further and should therefore be monitored and corrected. Moreover, the combination with other psychotropic or non-psychiatric medication with a risk of QT prolongation should be avoided (for a list see for example http://www.torsades.org).

5. **Hyperprolactinemia: asymptomatic hyperprolactinemia does not necessarily need treatment (C). Strategies to reduce hyperprolactinemia are dose reduction (C), change to a prolactin sparing antipsychotic (A), adding a partial dopamine agonist (A)**

   Justification: Hyperprolactinemia can be associated with sexual side-effects (e.g., amenorrhea, galactorrhea, loss of libido), osteoporosis (Kishimoto et al., 2012), and there is also an unresolved discussion about an increased risk for breast cancer (Haddad and Wieck, 2004). Some of these side-effects are, however, multifactorial. E.g. certain sexual side-effects, such as lack of libido, may be due to the negative symptoms of schizophrenia, and osteoporosis has also been associated with lack of physical activity due to the same symptoms. The experts feel that as long as hyperprolactinemia is asymptomatic, changes in antipsychotic drug treatment are not mandatory. In case of very high levels (i.e., >200 ng/dL), an endocrinologist may, however, be consulted. The risk for hyperprolactinemia of the various drugs differs enormously (see Table 1, and Leucht et al., 2013b). In RCTs, it has been shown that adding the partial dopamine agonist aripiprazole can reduce prolactin levels (Gallego et al., 2012).

6. **Seizures: reduce the dose (C), use an antipsychotic with less epileptogenic potential (C), add an antiepileptic (C)**

   Justification: Antipsychotic drugs differ in their propensity to reduce the seizure threshold. The literature stems mostly from case reports and retrospective analyses. These effects are dose dependent. Hedges et al., 2003 concluded that chlorpromazine has the greatest risk among the first-generation antipsychotic drugs and clozapine among the second-generation antipsychotics, while the risk of fluphenazine, haloperidol, molindone, pimozide, risperidone and trifluoperazine appears to be low. Other factors that should be considered are a history of seizure activity, combination with other seizure threshold lowering drugs, rapid dose increase and drug-drug interactions (Hedges et al., 2003).

7. **Liver enzyme elevation: monitor (C), if persistent, obtain medical check-up (C), reduce the dose (C), use an antipsychotic which is metabolized little by the liver and (mainly) excreted via the kidney (C)**

   Justification: liver enzyme elevation is frequent and often transient. If it persists or if levels are high, a medical check-up should be obtained. Dose reduction can be tried, and it can be

necessary to switch to a drug which is only very little metabolized by the liver, such as paliperidone, amisulpride and (less so) ziprasidone.

8. **Photosensitivity and other dermatologic side-effects: sun protection (limit sun exposure, use sun cream, protect skin with clothes) (C). Allergic reactions often make a switch of the antipsychotic necessary (C)**

   Justification: Antipsychotic drugs and other psychotropic agents can lead to photosensitivity and allergic reactions. The strategies to prevent or treat these conditions are pragmatic.

9. **Blood count changes: monitor (C), consider adding lithium, and monitor white count in the afternoon (C), change or stop medication (C), follow rules for agranulocytosis**

   Justification: transient leukopenia, leukocytosis, lymphocytosis, thrombocytopenia and eosinophilia do not require a change of treatment. Agranulocytosis is a life-threatening side-effect which often requires hematologic intensive care (definition: granulocytes < 1000/mm^3, complications must be expected with values < 500/mm^3). The incidence of this side-effect is highest for clozapine; therefore, when this drug is used, regular differential blood-counts must be taken, and if the white blood-count or granulocyte count falls below a certain threshold clozapine needs to be stopped. Patients also need to be informed about the symptoms of agranulocytosis, which often first manifests as a fever or infections such as a sore throat. Rechallenge after simple leucopenia is possible and often successful. Since leucocyte and granulocyte levels have diurnal variation, blood draws in the afternoon yield higher levels. As the exact recommendations differ locally, we need to refer to the recommendations in the different countries.

D) References

Agid, O., Kapur, S., Arenovich, T., Zipursky, R.B., 2003. Delayed-onset hypothesis of antipsychotic action - A hypothesis tested and rejected. Arch.Gen.Psychiatry 60, 1228-1235.

Akerele, E., Levin, F.R., 2007. Comparison of olanzapine to risperidone in substance-abusing individuals with schizophrenia. Am.J.Addict. 16, 260-268.

Akhondzadeh, S., Tabatbaee, M., Amini, H., Ahmadi Abhari, S.A., Abbasi, S.H., Behnam, B., 2007. Celecoxib as adjunctive therapy in schizophrenia: A double-blind, randomized and placebo-controlled trial. Schizophr.Res. 90, 179-185.

Alexander, J., Tharyan, P., Adams, C., John, T., Mol, C., Philip, J., 2004. Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting - Pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine. British Journal of Psychiatry 185, 63-69.

Allison, D.B., Mentore, J.L., Heo, M., Chandler, L.P., Cappelleri, J.C., Infante, M.C., Weiden, P.J., 1999. Antipsychotic-induced weight gain: A comprehensive research synthesis. Am.J.Psychiatry 156, 1686-1696.

Amato, L., Minozzi, S., Pani, P.P., Davoli, M., 2007. Antipsychotic medications for cocaine dependence. Cochrane Database Syst Rev, CD006306.

Andreasen, N., Carpenter, W., Kane, J., Lasser, R., Marder, S., Weinberger, D., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am.J.Psychiatry 62, 441-449.

Arango, C., Robles, O., Parellada, M., Fraguas, D., Ruiz-Sancho, A., Medina, O., Zabala, A., Bombin, I., Moreno, D., 2009. Olanzapine compared to quetiapine in adolescents with a first psychotic episode. European child & adolescent psychiatry 18, 418-428.
Ascher-Svanum, H., Nyhuis, A.W., Faries, D.E., Kinon, B.J., Baker, R.W., Shekhar, A., 2007. Clinical, Functional, and Economic Ramifications of Early Nonresponse to Antipsychotics in the Naturalistic Treatment of Schizophrenia. Schizophr.Bull.
Azima, H., Arthurs, D., Silver, A., 1962. The effects of chlordiazepoxide (librium) in anxiety states. A multi-blind study. Can Psychiatr Assoc J 7, 44-50.
Barbui, C., Saraceno, B., Liberati, A., Garattini, S., 1996. Low-dose neuroleptic therapy and relapse in schizophrenia: meta-analysis of randomized controlled trials. Eur.Psychiatry 11, 306-311.
Barbui, C., Signoretti, A., Mule, S., Boso, M., Cipriani, A., 2009. Does the Addition of a Second Antipsychotic Drug Improve Clozapine Treatment? Schizophrenia Bulletin 35, 458-468.
Basan, A., Leucht, S., 2004. Valproate for schizophrenia. Cochrane.Database.Syst.Rev., CD004028.
Battaglia, J., Moss, S., Rush, J., Kang, J., Mendoza, R., Leedom, L., Dubin, W., McGlynn, C., Goodman, L., 1997. Haloperidol, Lorazepam, or both for psychotic agitation: a multicenter, prospective, double blind, emergency department study. AMERICAN JOURNAL OF EMERGENCY MEDICINE 15, 335-340.
Bhidayasiri, R., Fahn, S., Weiner, W.J., Gronseth, G.S., Sullivan, K.L., Zesiewicz, T.A., American Academy of, N., 2013. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 81, 463-469.
Biederman, J., Lerner, Y., Belmaker, R.H., 1979. Combination of lithium carbonate and haloperidol in schizo-affective patients. Archives of General Psychiatry 36, 327-333.
Bollini, P., 1994. Antipsychotic drugs: is more worse? A meta analysis of the published randomized controlled trials. Psychol.Med. 24, 307-316.
Boter, H., Peuskens, J., Libiger, J., Fleischhacker, W.W., Davidson, M., Galderisi, S., Kahn, R.S., group, E.s., 2009. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). Schizophr Res 115, 97-103.
Buchanan, R.W., Conley, R.R., Dickinson, D., Ball, M.P., Feldman, S., Gold, J.M., McMahon, R.P., 2008. Galantamine for the treatment of cognitive impairments in people with schizophrenia. Am J Psychiatry 165, 82-89.
Buchanan, R.W., Kreyenbuhl, J., Kelly, D.L., Noel, J.M., Boggs, D.L., Fischer, B.A., Himelhoch, S., Fang, B., Peterson, E., Aquino, P.R., Keller, W., 2010. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr.Bull. 36, 71-93.
Caemmerer, J., Correll, C.U., Maayan, L., 2012. Acute and maintenance effects of non-pharmacologic interventions for antipsychotic associated weight gain and metabolic abnormalities: a meta-analytic comparison of randomized controlled trials. Schizophr Res 140, 159-168.
Caligiuri, M.R., Jeste, D.V., Lacro, J.P., 2000. Antipsychotic-Induced movement disorders in the elderly: epidemiology and treatment recommendations. Drugs & aging 17, 363-384.
Carpenter, W.T., Hanlon, T.E., Heinrichs, D.W., Summerfelt, A.T., Kirkpatrick, B., Levine, J., Buchanan, R.W., 1990. Continuous versus targeted medication in schizophrenic outpatients: outcome results. Am.J.Psychiatry 147, 1138-1163.
Casey, D.E., Carson, W.H., Saha, A., Liebeskind, A., Ali, M.W., Jody, D., Ingenitoon, G.G., group, A.s., 2003. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. Psychopharmacology 166, 391-399.
Casey, D.E., Daniel, D.G., Tamminga, C., Kane, J.M., Tran-Johnson, T., Wozniak, P., bi-Saab, W., Baker, J., Redden, L., Greco, N., Saltarelli, M., 2009. Divalproex ER combined with olanzapine or risperidone for treatment of acute exacerbations of schizophrenia. Neuropsychopharmacology 34, 1330-1338.
Chang, Y.C., Lane, H.Y., Yang, K.H., Huang, C.L., 2006. Optimizing early prediction for antipsychotic response in schizophrenia. J Clin Psychopharmacol 26, 554-559.
Cheine, M., Ahonen, J., Wahlbeck, K., 2003. Beta-blocker supplementation of standard drug treatment for schizophrenia (Cochrane Review). The Cochrane Library.

Chen, E.Y.H., Hui, C.L.M., Lam, M., Law, C.W., Chiu, C.P.Y., Chung, D.W.S., Tso, S., Pang, E.P.F., Chan, K.T., Wong, Y.C., Mo, F., Chan, K.P.M., Yao, T.J., Hung, S.F., Honer, W.G., 2010. A double-blind randomized placebo-controlled study of relapse prevention in remitted first-episode psychosis patients following one year of maintenance therapy. BMJ 341, c4024.
Cheung, H.K., 1981. Schizophrenics fully remitted on neuroleptics for 3-5 years - to stop or continue drugs? British Journal of Psychiatry 138, 490-494.
Chouinard, G., Jones, B.D., 1980. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry 137, 16-21.
Chua, W.L., Santiago, A.D., Kulkarni, J., Mortimer, A., 2005. Estrogen for schizophrenia. Cochrane Database of Systematic Reviews.
Cipriani, A., Barbui, C., Salanti, G., Rendell, J., Brown, R., Stockton, S., Purgato, M., Spineli, L.M., Goodwin, G.M., Geddes, J.R., 2011. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 378, 1306-1315.
Citrome, L., 2007a. Comparison of intramuscular ziprasidone, olanzapine, or aripiprazole for agitation: a quantitative review of efficacy and safety. J Clin.Psychiatry 68, 1876-1885.
Citrome, L., 2007b. The psychopharmacology of violence with emphasis on schizophrenia, part 1: acute treatment. J Clin Psychiatry 68, 163-164.
Citrome, L., 2007c. The psychopharmacology of violence with emphasis on schizophrenia, part 2: long-term treatment. J Clin Psychiatry 68, 331-332.
Citrome, L., 2007d. The psychopharmacology of violence with emphasis on schizophrenia, part 2: long-term treatment. J Clin Psychiatry 68, 331-332.
Citrome, L., Casey, D.E., Daniel, D.G., Wozniak, P., Kochan, L.D., Tracy, K.A., 2004. Adjunctive divalproex and hostility among patients with schizophrenia receiving olanzapine or risperidone. Psychiatr Serv 55, 290-294.
Citrome, L., Shope, C.B., Nolan, K.A., Czobor, P., Volavka, J., 2007. Risperidone alone versus risperidone plus valproate in the treatment of patients with schizophrenia and hostility. Int Clin Psychopharmacol 22, 356-362.
Correll, C., Agarwal, V., Kane, J., 2011. Gradual and Overlapping Antipsychotic Switch Strategies Are Associated with Less All-Cause Discontinuation in

Schizophrenia: Results from a Meta-analysis of Different Switch Strategies, ACNP 2011.
Correll, C.U., 2010. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. European psychiatry : the journal of the Association of European Psychiatrists 25 Suppl 2, S12-21.
Correll, C.U., Malhotra, A.K., Kaushik, S., McMeniman, M., Kane, J.M., 2003. Early prediction of antipsychotic response in schizophrenia. Am.J.Psychiatry 160, 2063-2065.
Correll, C.U., Manu, P., Olshanskiy, V., Napolitano, B., Kane, J.M., Malhotra, A.K., 2009a. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA 302, 1765-1773.
Correll, C.U., Penzner, J.B., Parikh, U.H., Mughal, T., Javed, T., Carbon, M., Malhotra, A.K., 2006. Recognizing and monitoring adverse events of second-generation antipsychotics in children and adolescents. Child and adolescent psychiatric clinics of North America 15, 177-206.
Correll, C.U., Rummel-Kluge, C., Corves, C., Kane, J.M., Leucht, S., 2009b. Antipsychotic Combinations vs Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials. Schizophr.Bull. 35, 443-457.
Correll, C.U., Schenk, E.M., 2008. Tardive dyskinesia and new antipsychotics. Curr.Opin.Psychiatry 21, 151-156.
Crocq, M.A., Naber, D., Lader, M.H., Thibaut, F., Drici, M., Everitt, B., Hall, G.C., Le Jeunne, C., Mittoux, A., Peuskens, J., Priori, S., Sturkenboom, M., Thomas, S.H., Tanghoj, P., Toumi, M., Mann, R., Moore, N.D., 2010. Suicide attempts in a prospective cohort of patients with schizophrenia treated with sertindole or risperidone. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 20, 829-838.

Crossley, N.A., Constante, M., McGuire, P., Power, P., 2010. Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. Br J Psychiatry 196, 434-439.
Davidson, M., Galderisi, S., Weiser, M., Werbeloff, N., Fleischhacker, W.W., Keefe, R.S., Boter, H., Keet, I.P., Prelipceanu, D., Rybakowski, J.K., Libiger, J., Hummer, M., Dollfus, S., Lopez-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rossler, A., Kahn, R.S., 2009. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). Am J Psychiatry 166, 675-682.
Davis, J.M., Chen, N., Glick, I.D., 2003. A meta-analysis of the efficacy of second-generation antipsychotics. Arch.Gen.Psychiatry 60, 553-564.
Davis, J.M., Mentalon, L., Watanabe, M.D., 1994. Depot antipsychotic drugs. Place in therapy. Drugs 47, 741-773.
De Hert, M., Cohen, D., Bobes, J., Cetkovich-Bakmas, M., Leucht, S., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Asai, I., Moller, H.J., Gautam, S., Detraux, J., Correll, C.U., 2011a. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World psychiatry : official journal of the World Psychiatric Association 10, 138-151.
de Hert, M., Correll, C.U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Moller, H.J., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Leucht, S., 2011b. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World psychiatry : official journal of the World Psychiatric Association 10, 52-77.
De Hert, M., Dobbelaere, M., Sheridan, E.M., Cohen, D., Correll, C.U., 2011c. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice. European psychiatry : the journal of the Association of European Psychiatrists 26, 144-158.
de Lucena, D., Fernandes, B.S., Berk, M., Dodd, S., Medeiros, D.W., Pedrini, M., Kunz, M., Gomes, F.A., Giglio, L.F., Lobato, M.I., Belmonte-de-Abreu, P.S., Gama, C.S., 2009. Improvement of negative and positive symptoms in treatment-refractory schizophrenia: a double-blind, randomized, placebo-controlled trial with memantine as add-on therapy to clozapine. J Clin Psychiatry 70, 1416-1423.
Dixon, L.B., Dickerson, F., Bellack, A.S., Bennett, M., Dickinson, D., Goldberg, R.W., Lehman, A., Tenhula, W.N., Calmes, C., Pasillas, R.M., Peer, J., Kreyenbuhl, J., Schizophrenia Patient Outcomes Research, T., 2010. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. Schizophr Bull 36, 48-70.
Dold, M., Fugger, G., Aigner, M., Lanzenberger, R., Kasper, S., 2015. Dose escalation of antipsychotic drugs in schizophrenia: a meta-analysis of randomized controlled trials. Schizophr Res 166, 187-193.
Dold, M., Li, C., Tardy, M., Khorsand, V., Gillies, D., Leucht, S., 2012. Benzodiazepines for schizophrenia, Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd.
Ehrenreich, H., Hinze-Selch, D., Stawicki, S., Aust, C., Knolle-Veentjer, S., Wilms, S., Heinz, G., Erdag, S., Jahn, H., Degner, D., Ritzen, M., Mohr, A., Wagner, M., Schneider, U., Bohn, M., Huber, M., Czernik, A., Pollmacher, T., Maier, W., Siren, A.L., Klosterkotter, J., Falkai, P., Ruther, E., Aldenhoff, J.B., Krampe, H., 2007. Improvement of cognitive functions in chronic schizophrenic patients by recombinant human erythropoietin. Molecular Psychiatry 12, 206-220.
Elias, A., Kumar, A., 2007. Testosterone for schizophrenia. Cochrane Database Syst Rev, CD006197.
Emsley, R., Fleischhacker, W.W., 2013. Is the ongoing use of placebo in relapse-prevention clinical trials in schizophrenia justified? Schizophr Res 150, 427-433.
Emsley, R.A., Group, R.W., 1999. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Schizophr.Bull. 25, 721-729.
Essock, S.M., Covell, N.H., Davis, S.M., Stroup, T.S., Rosenheck, R.A., Lieberman, J.A., 2006. Effectiveness of switching antipsychotic medications. Am J Psychiatry 163, 2090-2095.
Essock, S.M., Schooler, N.R., Stroup, T.S., McEvoy, J.P., Rojas, I., Jackson, C., Covell, N.H., Schizophrenia Trials, N., 2011. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry 168, 702-708.

Faulkner, G., Cohn, T., Remington, G., 2007. Interventions to reduce weight gain in schizophrenia, Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd.
Fleischhacker, W.W., Heikkinen, M.E., Olie, J.P., Landsberg, W., Dewaele, P., McQuade, R.D., Loze, J.Y., Hennicken, D., Kerselaers, W., 2010. Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: a randomized, double-blind, placebo-controlled trial. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 13, 1115-1125.
Fleischhacker, W.W., Uchida, H., 2014. Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 17, 1083-1093.
Fraguas, D., Correll, C.U., Merchan-Naranjo, J., Rapado-Castro, M., Parellada, M., Moreno, C., Arango, C., 2011. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 21, 621-645.
Gaebel, W., Riesbeck, M., Wolwer, W., Klimke, A., Eickhoff, M., von Wilmsdorff, M., Lemke, M., Heuser, I., Maier, W., Huff, W., Schmitt, A., Sauer, H., Riedel, M., Klingberg, S., Kopcke, W., Ohmann, C., Moller, H.J., German Study Group on First-Episode, S., 2011. Relapse prevention in first-episode schizophrenia--maintenance vs intermittent drug treatment with prodrome-based early intervention: results of a randomized controlled trial within the German Research Network on Schizophrenia. J Clin Psychiatry 72, 205-218.
Gallego, J.A., Nielsen, J., De Hert, M., Kane, J.M., Correll, C.U., 2012. Safety and tolerability of antipsychotic polypharmacy. Expert opinion on drug safety 11, 527-542.
Gallego, J.A., Robinson, D.G., Sevy, S.M., Napolitano, B., McCormack, J., Lesser, M.L., Kane, J.M., 2011. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? J Clin Psychiatry 72, 1691-1696.
Gardner, D.M., Murphy, A.L., O'Donnell, H., Centorrino, F., Baldessarini, R.J., 2010. International consensus study of antipsychotic dosing. Am J Psychiatry 167, 686-693.
Geddes, J., Freemantle, N., Harrison, P., Bebbington, P., 2000. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 321, 1371-1376.
Goodwin, G., Fleischhacker, W., Arango, C., Baumann, P., Davidson, M., de, H.M., Falkai, P., Kapur, S., Leucht, S., Licht, R., Naber, D., O'Keane, V., Papakostas, G., Vieta, E., Zohar, J., 2009. Advantages and disadvantages of combination treatment with antipsychotics ECNP Consensus Meeting, March 2008, Nice. Eur.Neuropsychopharmacol. 19, 520-532.
Gundlach, R., Engelhardt, D.M., Hankoff, L., Paley, H., Rudorfer, L., Bird, E., 1966. A double-blind outpatient study of diazepam (Valium) and placebo. Psychopharmacologia 9, 81-92.
Haddad, P.M., Wieck, A., 2004. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs 64, 2291-2314.
Hamann, J., Cohen, R., Leucht, S., Busch, R., Kissling, W., 2007. Shared decision making and long-term outcome in schizophrenia treatment. J Clin Psychiatry 68, 992-997.
Hamann, J., Leucht, S., Kissling, W., 2003. Shared decision making in psychiatry. Acta Psychiatrica Scandinavica 107, 403-409.
Hatta, K., Otachi, T., Sudo, Y., Hayakawa, T., Ashizawa, Y., Takebayashi, H., Hayashi, N., Hamakawa, H., Ito, S., Nakase, R., Usui, C., Nakamura, H., Hirata, T., Sawa, Y., Group, J.S., 2011. Difference in early prediction of antipsychotic non-response between risperidone and olanzapine in the treatment of acute-phase schizophrenia. Schizophr Res 128, 127-135.
Hatta, K., Otachi, T., Sudo, Y., Kuga, H., Takebayashi, H., Hayashi, H., Ishii, R., Kasuya, M., Hayakawa, T., Morikawa, F., Hata, K., Nakamura, M., Usui, C., Nakamura, H., Hirata, T., Sawa, Y., group, J.s., 2012. A comparison between augmentation with olanzapine and increased risperidone dose in acute schizophrenia patients showing early non-response to risperidone. Psychiatry Res 198, 194-201.
Hausmann, A., Fleischhacker, W.W., 2002. Differential diagnosis of depressed mood in patients with schizophrenia: a diagnostic algorithm based on a review. Acta Psychiatr Scand 106, 83-96.

Hedges, D., Jeppson, K., Whitehead, P., 2003. Antipsychotic medication and seizures: a review. Drugs of today (Barcelona, Spain : 1998) 39, 551-557.
Herz, M.I., Glazer, W.M., Mostert, M.A., Sheard, M.A., Szymanski, H.V., Hafez, H., Mirza, M., Vana, J., 1991. Intermittent vs maintenance medication in schizophrenia. Two-year results. Arch.Gen.Psychiatry 48, 333-339.
Hiemke, C., Baumann, P., Bergemann, N., Conca, A., Dietmaier, O., Egberts, K., Fric, M., Gerlach, M., Greiner, C., Grunder, G., Haen, E., Havemann-Reinecke, U., Jaquenoud Sirot, E., Kirchherr, H., Laux, G., Lutz, U.C., Messer, T., Muller, M.J., Pfuhlmann, B., Rambeck, B., Riederer, P., Schoppek, B., Stingl, J., Uhr, M., Ulrich, S., Waschgler, R., Zernig, G., 2011. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 44, 195-235.
Honer, W.G., MacEwan, G.W., Gendron, A., Stip, E., Labelle, A., Williams, R., Eriksson, H., Group, S.S., 2012. A randomized, double-blind, placebo-controlled study of the safety and tolerability of high-dose quetiapine in patients with persistent symptoms of schizophrenia or schizoaffective disorder. J Clin Psychiatry 73, 13-20.
Huf, G., Coutinho, E.S., Adams, C.E., 2007. Rapid tranquillisation in psychiatric emergency settings in Brazil: pragmatic randomised controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine. BMJ 335, 869.
Huf, G., Coutinho, E.S.F., Adams, C.E., Borges, R.V.S., Ferreira, M.A.V., Silva, F.J.F., Pereira, A.J.C.R., Abreu, A.M., Lugao, S.M., Santos, M.P.C.P., Gewandsznajder, M., Mercadante, V.R.P., Lange, W., Dias, C.L., Brasil, M.A., Huf, G., Coutinho, E.S.F., Adams, C.E., Fagundes, H.M., Lopez, J.R.R.A., Lima, M., Campos, M.B., Rozenfeld, S., Braz, R.M., Struchiner, C.J., Camacho, L.B., Mari, J.D., 2003. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. BRITISH MEDICAL JOURNAL 327, 708-711.
Jager, M., Schmauss, M., Laux, G., Pfeiffer, H., Naber, D., Schmidt, L.G., Gaebel, W., Klosterkotter, J., Heuser, I., Maier, W., Lemke, M.R., Degner, D., Buchkremer, G., Gastpar, M., Moller, H.J., Riedel, M., 2009. Early improvement as a predictor of remission and response in schizophrenia: Results from a naturalistic study. Eur.Psychiatry 24, 501-506.
Jolley, A.G., Hirsch, S.R., 1990. Trial brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: clinical and social outcome at two years. B.M.J. 301, 837-842.
Joy, C.B., Mumby-Croft, R., Joy, L.A., 2006. Polyunsaturated fatty acid supplementation for schizophrenia. Cochrane Database of Systematic Reviews.
Kane, J.M., Honigfeld, G., Singer, J., Meltzer, H., group, a.t.C.C.s., 1988. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Archives of General Psychiatry 45, 789-796.
Kane, J.M., Marder, S.R., Schooler, N.R., Wirshing, W.C., Umbricht, D., Baker, R.W., Wirshing, D.A., Safferman, A., Ganguli, R., McMeniman, M., Borenstein, M., 2001. Clozapine and haloperidol in moderately refractory schizophrenia - A 6-month randomized and double-blind comparison. Arch.Gen.Psychiatry 58, 965-972.
Keefe, R.S.E., Bilder, R.M., Davis, S.M., Harvey, P.D., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Capuano, G., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Roscnheck, R.A., Perkins, D.O., Davis, C.E., Hsiao, J.K., Lieberman, J.A., 2007. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. Arch.Gen.Psychiatry 64, 633-647.
Kim, J.H., Ryu, S., Nam, H.J., Lim, M., Baek, J.H., Joo, Y.H., Kwon, J.S., Ha, T.H., Hong, K.S., 2012. Symptom structure of antipsychotic-induced obsessive compulsive symptoms in schizophrenia patients. Prog Neuropsychopharmacol Biol Psychiatry 39, 75-79.
Kinon, B.J., Basson, B.R., Gilmore, J.A., Malcolm, S., Stauffer, V.L., 2000. Strategies for switching from conventional antipsychotic drugs or risperidone to olanzapine. J Clin Psychiatry 61, 833-840.
Kinon, B.J., Chen, L., scher-Svanum, H., Stauffer, V.L., Kollack-Walker, S., Zhou, W., Kapur, S., Kane, J.M., 2010. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. Neuropsychopharmacology 35, 581-590.
Kinon, B.J., Kane, J.M., Johns, C., Perovich, R., Ismi, M., Koreen, A., Weiden, P., 1993. Treatment of neuroleptic-resistant schizophrenic relapse. Psychopharmacol.Bull. 29, 309-314.

Kinon, B.J., scher-Svanum, H., Adams, D.H., Chen, L., 2008a. The temporal relationship between symptom change and treatment discontinuation in a pooled analysis of 4 schizophrenia trials. J.Clin.Psychopharmacol. 28, 544-549.
Kinon, B.J., Volavka, J., Stauffer, V., Edwards, S.E., Liu-Seifert, H., Chen, L., Adams, D.H., Lindenmayer, J.P., McEvoy, J.P., Buckley, P.F., Lieberman, J.A., Meltzer, H.Y., Wilson, D.R., Citrome, L., 2008b. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. J Clin.Psychopharmacol. 28, 392-400.
Kishi, T., Matsuda, Y., Iwata, N., Correll, C.U., 2013. Antipsychotics for cocaine or psychostimulant dependence: systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Psychiatry 74, e1169-1180.
Kishimoto, T., 2012. New results alter balance of evidence of meta-analysis on long-acting injectable vs. oral antipsychotics in schizophrenia Schizophr.Res. 136, S58.
Kishimoto, T., Agarwal, V., Kishi, T., Leucht, S., Kane, J.M., Correll, C.U., 2013a. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. Mol Psychiatry 18, 53-66.
Kishimoto, T., De Hert, M., Carlson, H.E., Manu, P., Correll, C.U., 2012. Osteoporosis and fracture risk in people with schizophrenia. Current opinion in psychiatry 25, 415-429.
Kishimoto, T., Nitta, M., Borenstein, M., Kane, J.M., Correll, C.U., 2013b. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry 74, 957-965.
Kissling, W., Kane, J.M., Barnes, T.R., Dencker, K., Fleischhacker, W.W., Goldstein, J.M., Johnson, D.A.W., Marder, S.R., Müller-Spahn, F., Tegeler, J., Wistedt, B., Woggon, B., 1991. Guidelines for neuroleptic relapse prevention in schizophrenia: Towards consensus view, in: Kissling, W. (Ed.), Guidelines for neuroleptic relapse prevention in schizophrenia. Springer, Heidelberg, Berlin, pp. 155-163.
Klein, E., Bental, E., Lerer, B., Belmaker, R.H., 1984. Carbamazepine and haloperidol v placebo and haloperidol in excited psychoses. A controlled study. Archives of General Psychiatry 41, 165-170.
Krakowski, M.I., Czobor, P., Citrome, L., Bark, N., Cooper, T.B., 2006. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch.Gen.Psychiatry 63, 622-629.
Kumra, S., Frazier, J.A., Jacobsen, L.K., McKenna, K., Gordon, C.T., Lenane, M.C., Hamburger, S.D., Smith, A.K., Albus, K.E., AlaghbandRad, J., Rapoport, J.L., 1996. Childhood-onset schizophrenia - A double-blind clozapine-haloperidol comparison. Archives of General Psychiatry 53, 1090-1097.
Kumra, S., Kranzler, H., Gerbino-Rosen, G., Kester, H.M., De Thomas, C., Kafantaris, V., Correll, C.U., Kane, J.M., 2008. Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. Biol Psychiatry 63, 524-529.
Lambert, M., Schimmelmann, B.G., Naber, D., Eich, F.X., Schulz, H., Huber, C.G., Karow, A., 2009. Early- and delayed antipsychotic response and prediction of outcome in 528 severely impaired patients with schizophrenia treated with amisulpride. Pharmacopsychiatry 42, 277-283.
Lee, J.G., Lee, S.W., Lee, B.J., Park, S.W., Kim, G.M., Kim, Y.H., 2012. Adjunctive memantine therapy for cognitive impairment in chronic schizophrenia: a placebo-controlled pilot study. Psychiatry investigation 9, 166-173.
Leucht, S., Arbter, D., Engel, R.R., Kissling, W., Davis, J.M., 2009a. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. Mol.Psychiatry 14, 429-447.
Leucht, S., Busch, R., Hamann, J., Kissling, W., Kane, J.M., 2005. Early onset of antipsychotic drug action: a hypothesis tested, confirmed and extended. Biol.Psychiatry 57, 1543-1549.
Leucht, S., Busch, R., Kissling, W., Kane, J.M., 2007a. Early prediction of antipsychotic non-response. J.Clin.Psychiatry 68, 352-360.
Leucht, S., Cipriani, A., Spineli, L.M., Mavridis, D., Örey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lässig, B., Salanti, G., Davis, J.M., 2013a. Multiple

treatments meta-analysis on the efficacy and tolerability of 15 antipsychotic drugs in schizophrenia. Lancet Accepted for publication.
Leucht, S., Cipriani, A., Spineli, L.M., Öerey, D., Richter, F., Samara, M., Barbui, C., Engel, R., Geddes, J., Kissling, W., Stapf, M.P., Lässig, B., Salanti, G., Davis, J.M., 2013b. Multiple treatments meta-analysis on the efficacy and tolerability of 15 antipsychotic drugs in schizophrenia. Lancet.
Leucht, S., Corves, C., Arbter, D., Engel, R.R., Li, C., Davis, J.M., 2009b. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 373, 31-41.
Leucht, S., Heres, S., Kissling, W., Davis, J.M., 2011. Evidence-based pharmacotherapy of schizophrenia. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 14, 269-284.
Leucht, S., Kissling, W., Engel, R.R., Davis, J.M., 2009c. Are new drugs for schizophrenia better than old ones? Reply. Lancet 373, 1249-1250.
Leucht, S., Kissling, W., McGrath, J., 2007b. Lithium for schizophrenia, Cochrane Database Syst.Rev. Wiley & Sons, p. CD003834.
Leucht, S., Komossa, K., Rummel-Kluge, C., Corves, C., Hunger, H., Schmid, F., Asenjo Lobos, C., Schwarz, S., Davis, J.M., 2009d. A meta-analysis of head to head comparisons of second generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 166, 152-163.
Leucht, S., McGrath, J., White, P., Kissling, W., 2007c. Carbamazapine for schizophrenia and schizoaffective psychoses. The Cochrane Library.
Leucht, S., Pitschel-Walz, G., Engel, R., Kissling, W., 2002. Amisulpride - an unusual atypical antipsychotic. A meta-analysis of randomized controlled trials. Am.J.Psychiatry 159, 180-190.
Leucht, S., Samara, M., Heres, S., Patel, M.X., Furukawa, T., Cipriani, A., Geddes, J., Davis, J.M., 2015a. Dose Equivalents for Second-Generation Antipsychotic Drugs: The Classical Mean Dose Method. Schizophr Bull.
Leucht, S., Samara, M., Heres, S., Patel, M.X., Woods, S.W., Davis, J.M., 2014. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr Bull 40, 314-326.
Leucht, S., Shamsi, A.S., Busch, R., Kissling, W., Kane, J.M., 2008. Early prediction of antipsychotic response. Replication and six weeks extension. Schizophr.Res., epub ahead of print.
Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., Davis, J.M., 2012. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 379, 2063-2071.
Leucht, S., Winter-van Rossum, I., Heres, S., Arango, C., Fleischhacker, W.W., Glenthoj, B., Leboyer, M., Leweke, F.M., Lewis, S., McGuire, P., Meyer-Lindenberg, A., Rujescu, D., Kapur, S., Kahn, R.S., Sommer, I.E., 2015b. The optimization of treatment and management of schizophrenia in Europe (OPTiMiSE) trial: rationale for its methodology and a review of the effectiveness of switching antipsychotics. Schizophr Bull 41, 549-558.
Levine, S.Z., Rabinowitz, J., Ascher-Svanum, H., Faries, D.E., Lawson, A.H., 2011. Extent of attaining and maintaining symptom remission by antipsychotic medication in the treatment of chronic schizophrenia: evidence from the CATIE study. Schizophr Res 133, 42-46.
Lieberman, J.A., Papadakis, K., Csernansky, J., Litman, R., Volavka, J., Jia, X.D., Gage, A., Group, M.-M.-S., 2009. A randomized, placebo-controlled study of memantine as adjunctive treatment in patients with schizophrenia. Neuropsychopharmacology 34, 1322-1329.
Lieberman, J.A., Phillips, M., Gu, H., Stroup, S., Zhang, P., Kong, L., Ji, Z.K.G., Hamer, R.M., 2003. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacology 28, 995-1003.
Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S.E., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N.Engl.J.Med. 353, 1209-1223.
Lima, A.R., Bacalcthuk, J., Barnes, T.R., Soares-Weiser, K., 2004a. Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev, CD001946.
Lima, A.R., Soares-Weiser, K., Bacaltchuk, J., Barnes, T.R., 2002. Benzodiazepines for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev, CD001950.

Lima, A.R., Weiser, K.V., Bacaltchuk, J., Barnes, T.R., 2004b. Anticholinergics for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev, CD003727.
Lin, C.H., Chou, L.S., Lin, C.H., Hsu, C.Y., Chen, Y.S., Lane, H.Y., 2007. Early prediction of clinical response in schizophrenia patients receiving the atypical antipsychotic zotepine. J.Clin.Psychiatry 68, 1522-1527.
Lindenmayer, J.P., Citrome, L., Khan, A., Kaushik, S., Kaushik, S., 2011. A randomized, double-blind, parallel-group, fixed-dose, clinical trial of quetiapine at 600 versus 1200 mg/d for patients with treatment-resistant schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 31, 160-168.
Lindenmayer, J.P., Khan, A., Iskander, A., Abad, M.T., Parker, B., 2007. A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. J Clin.Psychiatry 68, 368-379.
McClellan, J., Sikich, L., Findling, R.L., Frazier, J.A., Vitiello, B., Hlastala, S.A., Williams, E., Ambler, D., Hunt-Harrison, T., Maloney, A.E., Ritz, L., Anderson, R., Hamer, R.M., Lieberman, J.A., 2007. Treatment of early-onset schizophrenia spectrum disorders (TEOSS): rationale, design, and methods. Journal of the American Academy of Child and Adolescent Psychiatry 46, 969-978.
McEvoy, J.P., Byerly, M., Hamer, R.M., Dominik, R., Swartz, M.S., Rosenheck, R.A., Ray, N., Lamberti, J.S., Buckley, P.F., Wilkins, T.M., Stroup, T.S., 2014. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA 311, 1978-1987.
McEvoy, J.P., Hogarty, G.E., Steingard, S., 1991. Optimal dose of neuroleptic in acute schizophrenia. Arch.Gen.Psychiatry 48, 740-745.
Meltzer, H.Y., Alphs, L., Green, A.I., Altamura, A.C., Anand, R., Bertoldi, A., Bourgeois, M., Chouinard, G., Islam, M.Z., Kane, J., Krishnan, R., Lindenmayer, J.P., Potkin, S., 2003. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen.Psychiatry 60, 82-91.
Meltzer, H.Y., Bastani, B., Kwon, K.Y., Ramirez, L.F., Burnett, S., Sharpe, J., 1989. A prospective study of clozapine in treatment-resistant schizophrenic patients. I. Preliminary report. Psychopharmacology (Berl) 99 Suppl, S68-S72.
Miller, C.H., Fleischhacker, W.W., 2000. Managing antipsychotic-induced acute and chronic akathisia. Drug safety : an international journal of medical toxicology and drug experience 22, 73-81.
Minervini, M.G., Priore, P., Farolfi, A., Cesana, B., Morselli, P.L., 1990. Double blind, controlled study of the efficacy and safety of alpidem in the treatment of anxiety in schizophrenic in-patients. Pharmacopsychiatry 23, 102-106.
Mishara, A.L., Goldberg, T.E., 2004. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. Biol Psychiatry 55, 1013-1022.
Mizuno, Y., Suzuki, T., Nakagawa, A., Yoshida, K., Mimura, M., Fleischhacker, W.W., Uchida, H., 2014. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull 40, 1385-1403.
Moncrieff, J., 2006. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. Acta Psychiatr Scand 114, 3-13.
Morphy, M.A., 1986. A double-blind comparison of alprazolam and placebo in the treatment of anxious schizophrenic outpatients. Current therapeutic research 40, 551-560.
Muller, D.J., Kekin, I., Kao, A.C., Brandl, E.J., 2013. Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: update and report from a pharmacogenetic service clinic. International review of psychiatry 25, 554-571.
Nolte, S., Wong, D., Latchford, G., 2004. Amphetamines for schizophrenia. Cochrane Database of Systematic Reviews.
Organisation, W.H., 2010. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: Mental Health Gap Action Programme (mhGAP). World Health Organisation, Switzerland.

Petrakis, I.L., Nich, C., Ralevski, E., 2006. Psychotic spectrum disorders and alcohol abuse: a review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. Schizophr Bull 32, 644-654.
Petrides, G., Malur, C., Braga, R.J., Bailine, S.H., Schooler, N.R., Malhotra, A.K., Kane, J.M., Sanghani, S., Goldberg, T.E., John, M., Mendelowitz, A., 2015. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am J Psychiatry 172, 52-58.
Peuskens, J., Group., R.S., 1995. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Br.J.Psychiatry 166, 712-726.
Pietzcker, A., Gaebel, W., Koepcke, W., Linden, M., Mueller, P., Mueller-Spahn, F., Tegeler, J., 1993. Intermittent versus maintenance neuroleptic long-term treatment in schizophrenia - 2-year results of a German multicenter study. Journal of Psychiatric Research 27, 321-339.
Poyurovsky, M., 2010. Acute antipsychotic-induced akathisia revisited. Br J Psychiatry 196, 89-91.
Premkumar, T.S., Pick, J., 2006. Lamotrigine for schizophrenia. Cochrane Database Syst Rev, CD005962.
Rappard, F., Müller, N., 2004. Celecoxib Add-on Therapy Does Not Have Beneficial Antipsychotic Effects Over Risperidone Alone in Schizophrenia. Neuropsychopharmacology 29(Suppl 1), S222.
Rauch, A.S., Fleischhacker, W.W., 2013. Long-acting injectable formulations of new-generation antipsychotics: a review from a clinical perspective. Cns Drugs 27, 637-652.
Raveendran, N.S., Tharyan, P., Alexander, J., Adams, C.E., 2007. Rapid tranquillisation in psychiatric emergency settings in India: pragmatic randomised controlled trial of intramuscular olanzapine versus intramuscular haloperidol plus promethazine. BMJ 335, 865.
Remington, G., Chue, P., Stip, E., Kopala, L., Girard, T., Christensen, B., 2005. The crossover approach to switching antipsychotics: what is the evidence? Schizophr Res 76, 267-272.
Robinson, D., Woerner, M.G., Alvir, J.M., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Lieberman, J.A., 1999a. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 56, 241-247.
Robinson, D.G., Woerner, M.G., Alvir, J.M.J., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Bilder, R., Goldman, R., Lieberman, J.A., 1999b. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am.J.Psychiatry 156, 544-549.
Rosenheck, R., Cramer, J., Xu, W.C., Thomas, J., Henderson, W., Frisman, L., Fye, C., Charney, D., 1997. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. N.Engl.J.Med. 337, 809-815.
Rubio, G., Martinez, I., Ponce, G., Jimenez-Arriero, M.A., Lopez-Munoz, F., Alamo, C., 2006. Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. Canadian journal of psychiatry. Revue canadienne de psychiatrie 51, 531-539.
Rummel, C., Kissling, W., Leucht, S., 2006. Antidepressants for the negative symptoms of schizophrenia. Cochrane Database of Systematic Reviews.
Rybakowski, J.K., Vansteelandt, K., Remlinger-Molenda, A., Fleischhacker, W.W., Kahn, R.S., Peuskens, J., Group, E.S., 2014. Extrapyramidal symptoms during treatment of first schizophrenia episode: results from EUFEST. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 24, 1500-1505.
Saha, S., Chant, D., McGrath, J., 2007. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 64, 1123-1131.
Samaha, A.N., Seeman, P., Stewart, J., Rajabi, H., Kapur, S., 2007. Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. The Journal of neuroscience : the official journal of the Society for Neuroscience 27, 2979-2986.
Samara, M.T., Leucht, C., Leeflang, M.M., Anghelescu, I.G., Chung, Y.C., Crespo-Facorro, B., Elkis, H., Hatta, K., Giegling, I., Kane, J.M., Kayo, M., Lambert, M., Lin, C.H., Moller, H.J., Pelayo-Teran, J.M., Riedel, M., Rujescu, D., Schimmelmann, B.G., Serretti, A., Correll, C.U., Leucht, S., 2015. Early

Improvement As a Predictor of Later Response to Antipsychotics in Schizophrenia: A Diagnostic Test Review. Am J Psychiatry 172, 617-629.
Sampath, G., Shah, A., Krska, J., Soni, S.D., 1992. Neuroleptic discontinuation in the very stable schizophrenic patient - relapse rates and serum neuroleptic levels. Human Psychopharmacology 7, 255-264.
Sayers, S.L., Campbell, E.C., Kondrich, J., Mann, S.C., Cornish, J., O'Brien, C., Caroff, S.N., 2005. Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol. J.Nerv.Ment.Dis. 193, 379-386.
Scheltema Beduin, A.A., Swets, M., Machielsen, M., Korver, N., Genetic, R., Outcome of Psychosis, I., 2012. Obsessive-compulsive symptoms in patients with schizophrenia: a naturalistic cross-sectional study comparing treatment with clozapine, olanzapine, risperidone, and no antipsychotics in 543 patients. J Clin Psychiatry 73, 1395-1402.
Schennach-Wolff, R., Seemuller, F.H., Mayr, A., Maier, W., Klingberg, S., Heuser, I., Klosterkotter, J., Gastpar, M., Hafner, H., Sauer, H., Schneider, F., Gaebel, W., Jager, M., Moller, H.J., Riedel, M., 2010. An early improvement threshold to predict response and remission in first-episode schizophrenia. Br J Psychiatry 196, 460-466.
Schimmelmann, B.G., Schmidt, S.J., Carbon, M., Correll, C.U., 2013. Treatment of adolescents with early-onset schizophrenia spectrum disorders: in search of a rational, evidence-informed approach. Current opinion in psychiatry 26, 219-230.
Schirmbeck, F., Zink, M., 2012. Clozapine-induced obsessive-compulsive symptoms in schizophrenia: a critical review. Current neuropharmacology 10, 88-95.
Schooler, N.R., Keith, S.J., Severe, J.B., Matthews, S.M., Bellack, A.S., Glick, I.D., Hargreaves, W.A., Kane, J.M., Ninan, P.T., Frances, A., Jacobs, M., Lieberman, J.A., Mance, R., Simpson, G.M., Woerner, M.G., 1997. Relapse and rehospitalization during maintenance treatment of schizophrenia. Arch.Gen.Psychiatry 54, 453-463.
Sepehry, A.A., Potvin, S., Elie, R., Stip, E., 2007. Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: a meta-analysis. J.Clin.Psychiatry 68, 604-610.
Shalev, A., Hermesh, H., Rothberg, J., Munitz, H., 1993. Poor Neuroleptic Response in Acutely Exacerbated Schizophrenic-Patients. Acta Psychiatrica Scandinavica 87, 86-91.
Shepherd, M., Watt, D., Falloon, I., Smeeton, N., 1989. The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. Psychol.Med.Suppl. 15, 1-46.
Sherwood, M., Thornton, A.E., Honer, W.G., 2012. A quantitative review of the profile and time course of symptom change in schizophrenia treated with clozapine. J Psychopharmacol 26, 1175-1184.
Sikich, L., 2008. Efficacy of atypical antipsychotics in early-onset schizophrenia and other psychotic disorders. J Clin Psychiatry 69 Suppl 4, 21-25.
Sikich, L., Frazier, J.A., McClellan, J., Findling, R.L., Vitiello, B., Ritz, L., Ambler, D., Puglia, M., Maloney, A.E., Michael, E., De Jong, S., Slifka, K., Noyes, N., Hlastala, S., Pierson, L., McNamara, N.K., Delporto-Bedoya, D., Anderson, R., Hamer, R.M., Lieberman, J.A., 2008. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. Am J Psychiatry 165, 1420-1431.
Silvestri, S., Seeman, M.V., Negrete, J.C., Houle, S., Shammi, C.M., Remington, G.J., Kapur, S., Zipursky, R.B., Wilson, A.A., Christensen, B.K., Seeman, P., 2000. Increased dopamine D2 receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study. Psychopharmacology 152, 174-180.
Siris, S.G., 1993. Adjunctive medication in the maintenance treatment of schizophrenia and its conceptual implications. British Journal of Psychiatry 163, 22-78.
Smith, R.C., Infante, M., Singh, A., Khandat, A., 2001. The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. Int.J.Neuropsychopharmacol. 4, 239-250.

Sommer, I.E., Begemann, M.J., Temmerman, A., Leucht, S., 2011. Pharmacological Augmentation Strategies for Schizophrenia Patients With Insufficient Response to Clozapine: A Quantitative Literature Review. Schizophr Bull.
Sommer, I.E., de Witte, L., Begemann, M., Kahn, R.S., 2012. Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis. J Clin Psychiatry 73, 414-419.
Stip, E., Sepehry, A.A., Chouinard, S., 2007. Add-on therapy with acetylcholinesterase inhibitors for memory dysfunction in schizophrenia: a systematic quantitative review, part 2. Clin.Neuropharmacol. 30, 218-229.
Stroup, T.S., Lieberman, J.A., McEvoy, J.P., Swartz, M.S., Davis, S.M., Capuano, G.A., Rosenheck, R.A., Keefe, R.S.E., Miller, A.L., Belz, I., Hsiao, J.K., 2007. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: A CATIE study. Am.J.Psychiatry 164, 415-427.
Stroup, T.S., McEvoy, J.P., Ring, K.D., Hamer, R.H., LaVange, L.M., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Nussbaum, A.M., Lieberman, J.A., Schizophrenia Trials, N., 2011. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). Am J Psychiatry 168, 947-956.
Suzuki, T., Uchida, H., Watanabe, K., Nomura, K., Takeuchi, H., Tomita, M., Tsunoda, K., Nio, S., Den, R., Manki, H., Tanabe, A., Yagi, G., Kashima, H., 2007. How effective is it to sequentially switch among Olanzapine, Quetiapine and Risperidone?--A randomized, open-label study of algorithm-based antipsychotic treatment to patients with symptomatic schizophrenia in the real-world clinical setting. Psychopharmacology (Berl) 195, 285-295.
Taylor, D.M., Smith, L., Gee, S.H., Nielsen, J., 2012. Augmentation of clozapine with a second antipsychotic - a meta-analysis. Acta Psychiatr Scand 125, 15-24.
Tharyan, P., Adams, C.E., 2005. Electroconvulsive therapy for schizophrenia (Cochrane Review). The Cochrane Library.
Tiihonen, J., Haukka, J., Taylor, M., Haddad, P.M., Patel, M.X., Korhonen, P., 2011. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 168, 603-609.
Tiihonen, J., Wahlbeck, K., Kiviniemi, V., 2009. The efficacy of lamotrigine in clozapine-resistant schizophrenia: A systematic review and meta-analysis. Schizophr.Res. 109, 10-14.
Tiihonen, J., Wahlbeck, K., Lonnqvist, J., Klaukka, T., Ioannidis, J.P.A., Volavka, J., Haukka, J., 2006. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ 333, 224-227.
Trikalinos, T.A., Churchill, R., Ferri, M., Leucht, S., Tuunainen, A., Wahlbeck, K., Ioannidis, J.P.A., 2004. Effect sizes in cumulative meta-analyses of mental health randomized trials evolved over time. J.Clin.Epidemiol. 57, 1124-1130.
Tuominen, H.J., Tiihonen, J., Wahlbeck, K., 2006. Glutamatergic drugs for schizophrenia. Cochrane Database of Systematic Reviews.
Uchida, H., Suzuki, T., Takeuchi, H., Arenovich, T., Mamo, D.C., 2009. Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis. Schizophr.Bull. epub ahead of print.
Van Putten, T., 1978. Akinetic depression in schizophrenia. Arch.Gen.Psychiatry 35, 1101-1107.
Volavka, J., Czobor, P., Derks, E.M., Bitter, I., Libiger, J., Kahn, R.S., Fleischhacker, W.W., Group, E.S., 2011. Efficacy of antipsychotic drugs against hostility in the European First-Episode Schizophrenia Trial (EUFEST). J Clin Psychiatry 72, 955-961.
Wahlbeck, K., Cheine, M., Essali, M.A., Rezk, E., 1999. Clozapine vs typical neuroleptic medication for schizophrenia. Cochrane Database Syst.Rev. 2, CD000059.
Wang, C.Y., Xiang, Y.T., Cai, Z.J., Weng, Y.Z., Bo, Q.J., Zhao, J.P., Liu, T.Q., Wang, G.H., Weng, S.M., Zhang, H.Y., Chen, D.F., Tang, W.K., Ungvari, G.S., Risperidone Maintenance Treatment in

Schizophrenia, i., 2010. Risperidone maintenance treatment in schizophrenia: a randomized, controlled trial. Am J Psychiatry 167, 676-685.
Waraich, P., Adams, C., Hammill, K., Marti, J., Roque, M., 2002. Haloperidol dose for the acutely ill phase of schizophrenia. Cochrane Database Syst.Rev. 2, CD001951.
Whitehead, C., Moss, S., Cardno, A., Lewis, G., 2003. Antidepressants for the treatment of depression in people with schizophrenia: a systematic review. Psychol.Med. 33, 589-599.
Woodward, N.D., Purdon, S.E., Meltzer, H.Y., Zald, D.H., 2005. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine and risperidone in schizophrenia. Int.J.Neuropsychopharmacol. 8, 1-16.
Wunderink, L., Nieboer, R.M., Wiersma, D., Sytema, S., Nienhuis, F.J., 2013. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA psychiatry 70, 913-920.
Wunderink, L., Nienhuis, F.J., Sytema, S., Slooff, C.J., Knegtering, R., Wiersma, D., 2007. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. J Clin.Psychiatry 68, 654-661.
Zhang, J.P., Gallego, J.A., Robinson, D.G., Malhotra, A.K., Kane, J.M., Correll, C.U., 2012. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum, 1-14.
Zhang, J.P., Lencz, T., Malhotra, A.K., 2010. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. Am J Psychiatry 167, 763-772.
Zimbroff, D.L., Kane, J.M., Tamminga, C.A., Daniel, D.G., Mack, R.J., Wozniak, P.J., Sebree, T.B., Wallin, B.A., Kashkin, K.B., Adan, F., Ainslie, G., Allan, E., Atri, P., Baker, R., Beitman, B., Brown, G., Canive, J., Carman, J., Dott, S., Edwards, J., Fenton, W., Freidli, J., Funderburg, L., Ereshefsky, L., Gladson, M., Hamilton, J., Haque, S., Hartford, J., Horne, R., Houck, C., Jampala, C., Labelle, A., Larson, G., Liesem, M., Liskow, B., Makela, E., Moore, N., Morphy, M., Posever, T., Risch, S., Rotrosen, J., Sheehan, D., Silverstone, P., Swann, A., Tapp, A., Thomas, M., Volavka, J., Vora, S., 1997. Controlled, dose response study of sertindole and haloperidol in the treatment of schizophrenia. Am.J.Psychiatry 154, 782-791.
Zipursky, R.B., Menezes, N.M., Streiner, D.L., 2014. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. Schizophr Res 152, 408-414.