# Advantages and disadvantages of combination treatment with antipsychotics
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**Abstract**

Terminology and principles of combining antipsychotics with a second medication. The term "combination" includes virtually all the ways in which one medication may be added to another. The other commonly used terms are "augmentation" which implies an additive effect from

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adding a second medicine to that obtained from prescribing a first, an "add on" which implies adding on to existing, possibly effective treatment which, for one reason or another, cannot or should not be stopped. The issues that arise in all potential indications are: a) how long it is reasonable to wait to prove insufficiency of response to monotherapy; b) by what criteria that response should be defined; c) how optimal is the dose of the first monotherapy and, therefore, how confident can one be that its lack of effect is due to a truly inadequate response?

Before one considers combination treatment, one or more of the following criteria should be met; a) monotherapy has been only partially effective on core symptoms; b) monotherapy has been effective on some concurrent symptoms but not others, for which a further medicine is believed to be required; c) a particular combination might be indicated de novo in some indications; d) The combination could improve tolerability because two compounds may be employed below their individual dose thresholds for side effects. Regulators have been concerned primarily with a and, in principle at least, c above. In clinical practice, the use of combination treatment reflects the often unsatisfactory outcome of treatment with single agents.

Antipsychotics in mania. There is good evidence that most antipsychotics tested show efficacy in acute mania when added to lithium or valproate for patients showing no or a partial response to lithium or valproate alone. Conventional 2-armed trial designs could benefit from a third antipsychotic monotherapy arm.

In the long term treatment of bipolar disorder, in patients responding acutely to the addition of quetiapine to lithium or valproate, this combination reduces the subsequent risk of relapse to depression, mania or mixed states compared to monotherapy with lithium or valproate. Comparable data is not available for combination with other antipsychotics.

Antipsychotics in major depression. Some atypical antipsychotics have been shown to induce remission when added to an antidepressant (usually a SSRI or SNRI) in unipolar patients in a major depressive episode unresponsive to the antidepressant monotherapy. Refractoriness is defined as at least 6 weeks without meeting an adequate pre-defined treatment response. Long term data is not yet available to support continuing efficacy.

Schizophrenia. There is only limited evidence to support the combination of two or more antipsychotics in schizophrenia. Any monotherapy should be given at the maximal tolerated dose and at least two antipsychotics of different action/tolerability and clozapine should be given as a monotherapy before a combination is considered.

The addition of a high potency D2/3 antagonist to a low potency antagonist like clozapine or quetiapine is the logical combination to treat positive symptoms, although further evidence from well conducted clinical trials is needed. Other mechanisms of action than D2/3 blockade, and hence other combinations might be more relevant for negative, cognitive or affective symptoms.

Obsessive–compulsive disorder. SSRI monotherapy has moderate overall average benefit in OCD and can take as long as 3 months for benefit to be decided. Antipsychotic addition may be considered in OCD with tic disorder and in refractory OCD. For OCD with poor insight (OCD with "psychotic features"), treatment of choice should be medium to high dose of SSRI, and only in refractory cases, augmentation with antipsychotics might be considered. Augmentation with haloperidol and risperidone was found to be effective (symptom reduction of more than 35%) for patients with tics. For refractory OCD, there is data suggesting a specific role for haloperidol and risperidone as well, and some data with regard to potential therapeutic benefit with olanzapine and quetiapine.

Antipsychotics and adverse effects in severe mental illness. Cardio-metabolic risk in patients with severe mental illness and especially when treated with antipsychotic agents are now much better recognized and efforts to ensure improved physical health screening and prevention are becoming established.

# 1. Background

Antipsychotics are widely prescribed in psychiatry. Their use is, in many cases, as a combination. This arises from their co-prescribing with other medications or the combining of one antipsychotic with another. This is common in all the major indications such as schizophrenia, affective disorder and OCD. It occurs with both the typical and atypical antipsychotics (so-called because of their differential propensity for motor side effects). We recognize that terminology in this area has become controversial, but the use of the term atypical has the virtue that it reflects a desired pharmacological effect (Leucht et al., 2009). The rationale for combination treatments is usually one of the following:

a) Another or other treatment have been only partially effective on core symptoms.
b) Another or other treatments have been effective on core target symptoms, but for some other concurrent symptoms, a further medicine is believed to be required.

c) A particular combination might be beneficial de novo in some indications.
d) The combination could improve tolerability because two compounds may be employed below their individual dose thresholds for side effects.

The use of antipsychotics in combination with other drugs has been poorly investigated both by industry supported trials and by independent studies. Industry conducts most trials with monotherapy, and where combinations are used the purposes are variable. Regulators have been concerned primarily with a and, in principle at least, c above. Clinicians use combinations as often as or more often than monotherapy. They clearly believe that monotherapy frequently fails to produce an adequate response, and conduct endless "n of one" combination studies in individual patients. This implies a widespread failure to meet patients' needs with monotherapy. The investigation of combinations viewed in this light is highly under-valued at present and an the imperative to underpin common practice with an adequate research base should be better recognized. Accordingly this consensus was convened to allow a summary and discussion of the existing data and the possible trial designs that could underpin future use of drug combinations. The discussion was limited to the use of antipsychotics to enhance the focus. In drafting this document we have been mindful both of the need to validate assumptions and claims for efficacy in specific patient populations and the parallel need to ensure that safety issues are addressed both in the short and the long term.

## 2. Terminology and general considerations

A variety of terminology is used to describe the co-prescription of different medications. The most neutral is perhaps "combination" which includes virtually all the ways in which one medication may be added to another and, in particular, the de novo prescription of combinations. The other commonly used terms are "augmentation" which implies an additive effect from adding a second medicine to that obtained from prescribing a first, sometimes with the implication that the augmenting agent is alone unlikely to be fully effective. An "add on" implies adding on to existing, possibly effective treatment which, for one reason or another, cannot or should not be stopped. We will not discuss specific add-on medications given with the aim to reduce antipsychotic induced adverse events (for instance anticholinergics, lipid lowering drugs, etc.).

As indicated above, the typical scenario is a desire for increased efficacy. This may be because of the actual insufficient response of a single agent or the known likely insufficient response to a single agent, let us say A. Another reasons for the introduction of a second drug is when the patient shows some response to drug A, but suffers from adverse effects so its dose cannot be increased and a second drug with a different pharmacological profile is then added. No matter the indication, the issues that then arise are:

1) How long it is reasonable to wait to prove insufficiency of response.
2) By what criteria that response should be defined; in other words what scale or what level of clinical severity should determine lack of response?

3) How optimal is the dose of medicine A and, therefore, how confident can one be that its lack of effect is due to a truly inadequate response?

Another medicine, say B, is added and may be continued in either the short or the long term with the necessary implications for observing both efficacy and safety. This is a general scenario and it demands particular solutions for particular problems within each disorder. Furthermore, there will be requirements for pharmacological justification of potential phamacodynamic (PD) and pharmacokinetic (PK) interactions for both effects and adverse effects. Finally, there are general issues relating to study design:

1) Doses to be used.
2) Comparator required, if trials are to be conducted.
3) Endpoint: for example, if results of monotherapy were insufficient, should one aim for remission?
4) Duration of study.

The worked examples below illustrate the extent both to which experience exists (and evidence therefore underpins practice) and the extent to which it does not. A full review of the relevant literature will not be provided.

## 3. Pharmacodynamic properties of antipsychotics

Antipsychotics joined modern medicine in 1952, and over the half-century they have seen an evolving wave of use—from their early use as "tranquillisers" across a broad class of human distress, to the 1980s where their use became more restricted as "antipsychotics" (and mainly as antischizophrenia agents, largely driven by fears of tardive dyskinesia (TD)), to their burgeoning use outside schizophrenia and mania in the 2000s. What is their mechanism of action, how may it be augmented and how may antipsychotics augment the actions of other drugs?

While there are some controversies, the prevailing opinion is that the dopamine D2/3 blocking properties of antipsychotics are the most critical (and the single common feature) of all antipsychotics. This is the mechanism likely to determine their primary efficacy on positive symptoms in psychosis (Kapur et al., 2006). Three key questions need to be addressed. First, an empirical one: in which conditions does the addition of an antipsychotic further improve or enhance response? Secondly, is this response a specific property of a particular antipsychotic or is it seen across the entire class of antipsychotics? And, thirdly, what is their mechanism beyond psychosis: in mania, bipolar euthymia, unipolar and bipolar depression. Is it the same D2/3 blockade that works in all these conditions? In addition, mechanisms of action other than D2/3 antagonism may be more relevant for negative, cognitive or affective symptoms in schizophrenia.

In large measure, these questions are easier to ask than to answer. However, the most specific hypothesis is that under some circumstances the D2/3 receptor occupancy is insufficient to allow efficacy on positive symptoms. Amisulpride then provides an interesting tool for augmentation. It has a very specific pharmacology (D2/3 blocker), and little potential for pharmacokinetic interaction. Therefore successful

augmentation with amisulpiride supports a D2/3 receptor occupancy hypothesis (Moller, 2003). In other combinations when one antipsychotic is added to another, D2/3 occupancy is unlikely to be limiting, and the combination will have a much less certain or predictable pharmacology. Combination is then achieving a more complex polypharmacy than can be achieved by a single agent.

The most critical issue for the field will be to distinguish those effects and mechanisms that are generalizable and seen across antipsychotics, versus those efficacies that are seen only for specific agents. However, the following general hypotheses can be stated:

1) $D_{2/3}$ blockade can probably explain several of the augmenting effects of antispsychotics, but higher levels of $D_{2/3}$ blockade can produce subjective dysphoria and other subjective negative symptoms (even when they do not produce EPS or TD) and should be avoided (de Haan et al., 2000; Mizrahi et al., 2007).
2) The serotonergic properties of the atypical antipsychotics would likely add superiority to their affective profile (Meltzer, 1999); however, with multiple receptors come multiple side-effects.
3) Combining medications has the potential to increase adverse effects. This seems commonly to occur in practice.

It is unlikely that these mechanistic dilemmas will be resolved soon, so it will be critical to consider the receptor profile of the particular antipsychotic, dose (vis-à-vis its antipsychotic dose), potential active metabolites and the possibility of a pharmacokinetic interaction between the augmenting antipsychotic and the primary agent whenever considering augmentation trials.

## 4. Pharmacokinetics

Combining any medications, particularly those heavily metabolised before excretion, runs the risk of interactions that will elevate or reduce observed levels above or below those to be expected in monotherapy. Quite simply if drug B reduces the clearance of drug A, its levels will rise and its time to steady state will increase. It has long been known that clozapine in the presence of fluvoxamine shows a dramatic, tenfold increase in potential dose (Hiemke et al., 1994). Any antipsychotic such as clozapine and, to some extent, olanzapine with significant anticholinergic effects has the potential for toxicity at higher dose levels. Our experience of such drugs is driven primarily by tricyclic antidepressants where the therapeutic window is usually described as being between 150 and 250 ng/ml with levels of 450 risking EG changes and up to 1000 cognitive disturbances, delirium, convulsions, coma and death (Preskorn and Jerkovich, 1990). Therapeutically optimal plasma concentrations have been defined for some antipsychotics (Baumann et al., 2004; Mauri et al., 2007), although there is little support for routine plasma level monitoring.

Table 1 shows the pharmacokinetic and metabolic properties of the atypical antipsychotics. The common mechanisms of metabolism result from different affinities for specific cytochrome P450s enzymes. Since these are common pathways for drug metabolism they represent nodes at which there can be important interactions. Most antipsychotics with the notable exception of amisulpride are substrates of one or several forms of cytochrome P-450, but none of them is considered as a strong inhibitor of this type of enzyme. In contrast, antipsychotics which are CYP substrates may undergo inhibition (e.g. by fluoxetine for CYP2D6 substrates) or induction

**Table 1** Pharmacokinetic and metabolic properties of atypical antipsychotic drugs.

| Drug and active (inactive) metabolite | Half-life (h) in plasma | Oral bioavailability (%) | Cytochrome P-450 substrate |
|---|---|---|---|
| Amisulpride | 12 | 33–45 | – |
| Aripiprazole | 58–79* | 87 | 3A4, 2D6 |
|   Dehydroaripiprazole | 94 | | |
| Clozapine | 8.1–13.7 | 50–60 | 1A2, 3A4, 2C19, (2D6) |
|   Demethylclozapine | 5.5–35 | | |
|   (Clozapine N-oxide) | | | |
| Olanzapine | 27–39 | 80 | 1A2, (2D6) |
|   (N-glucuronide (main metab.)) | | | |
|   (N-oxide, demethylolanzapine) | | | |
| Paliperidone (9-OH-risperidone) | 23 | 28 | – |
| Quetiapine | 5.8–6.8 | 9 | 3A4, (2D6) |
|   (7-OH-quetiapine) | | | |
|   (Quetiapine sulfoxide) | | | |
|   Norquetiapine | | | |
| Risperidone | 2.8±0.5* | 66 | 2D6, 3A4 |
|   9-OH-risperidone | 20.5±2.9 | | (3A4) |
| Sertindole | 73–93 | 74 | 2D6, 3A4 |
|   Norsertindole | 242±222 | | |
| Ziprasidone | 3–10 | 59 | 3A4, 2C19 |
|   S-methyl-dihydroziprasidone | | | |
|   (Zipras. sulfoxide and sulfone) | | | |
| Zotepine | 15–24 | 10 | 1A2, 3A4, 2D6 |
|   Norzotepine | 19 | | |

*In extensive metabolisers (EM CYP2D6).

(e.g. carbamazepine for CYP3A substrates) of their metabolism by other drugs, which may result in modifications of their plasma concentrations and in clinically relevant consequences. As some CYP forms such as CYP2D6, CYP2C19 and CYP3A5 display genetic polymorphisms (Ingelman-Sundberg, 2004), there is a wide individual variability in the metabolism of the concerned drugs depending on the pharmacogenetic status of the patient (Dahl, 2002). Adaptation of the antipsychotic dose is recommended, as illustrated in Table 1 with regard to antipsychotics metabolised by CYP2D6 (Kirchheiner et al., 2004).

The plasma half lives of most of the atypical psychotics are between 5 and 40 h with the exceptions being sertindole and aripriprazole which are more slowly metabolised having half lives of between 50 and 100 h. The half life of some atypical antipsychotics may depend critically on the genetic status of the patient: e.g. risperidone in relation to CYP2 D6. In principle, any combination treatment must take into account the potential for co-medication to act either as an inhibitor of drug metabolism (delaying clearance and having the potential to lead to toxic levels of the index drug) or being an inducer of drug metabolism (increasing clearance and therefore leading to ineffective levels). Depending on their size, such effects may or may not move concentrations outside the therapeutic window.

For many decades, it was thought that the transport of drugs from the intestine in the blood and from the periphery in the brain occurred mainly by diffusional processes. The recent description of membrane proteins which act as transport molecules also has implications in psychopharmacology. For the basic psychotropic drugs which comprise many antipsychotics and antidepressants, P-glycoprotein, a member of the adenosine triphosphate-binding cassette (ABC) superfamily of transport proteins, functions as an efflux pump in different organs such as the gastrointestinal tract and at the blood brain barrier. P-glycoprotein may therefore limit the access of drugs to the brain, which are its substrates, and there is evidence that antipsychotic drugs like risperidone and 9-OH-risperidone are substrates. Therefore, inhibitors or inducers of P-glycoprotein may increase or decrease, respectively, the transport of these psychotropic drugs into the brain. P-glycoprotein displays genetic polymorphism. The exemplar drug nortriptyline will produce hypotension predictably in those individuals with a particular P-glycoprotein pharmacogenetic status (Ingelman-Sundberg, 2004; Kennedy et al., 2001). However, clinical studies to document the clinical and pharmacological consequences of both the genetic polymorphism and the interaction potential of P-glycoprotein are rare to this point (Ebinger and Uhr, 2006; Linnet and Ejsing, 2008; Marzolini et al., 2004).

The risk for interactions between antipsychotics and other drugs is well documented in the literature (Besag and Berry, 2006; Brown et al., 2004; Murray, 2006; Prior and Baker, 2003; Spina and de Leon, 2007; Wang et al., 2006). Such interactions are best investigated at steady state and the protocols are relatively well defined. Thus, in healthy volunteers with known cytochrome P450 and P-glycoprotein genotype/phenotype, treatment would be with an antipsychotic drug to study state conditions (4–5 half lives). Any augmenting drug should then be added similarly to study state conditions without other co-medication. In general a 12 h sampling period will allow calculation of the usual descriptive pharmacokinetic parameters, $C_{max}$, AUC and T-1/2. Empirical examinations of this kind have shown for example that valproate levels are somewhat reduced by quetiapine co-medication whereas the $C_{max}$ of quetiapine itself is enhanced in the presence of valproate. The mechanisms underlying these effects are not understood and the magnitude of the effects is not particularly large (Winter et al., 2007).

Clearly, an interaction implicating a particular CYP-isozyme should not occur in a patient lacking this enzyme for genetic reasons. This explains why any study would be best carried out in genotyped subjects. Single dose experiments may also give some useful information but steady-state conditions better reflect clinical conditions. Moreover, the advantage of having steady-state conditions is also valid for metabolites, which often do not reach relevant concentrations after a single dose of the parent compound, but whose effect may be important after repeated drug administration.

## 5. Mania

In clinical trials of monotherapy with the antipsychotics, response rates at 3 weeks are rarely greater than 60%. Systematic review of trials of all atypical antipsychotics suggest a number needed to treat (NNT) of about 5 at 6 weeks and 4 at 12 weeks. NNT of 4 equates to an absolute response rate of 25% greater for drug than placebo (Derry and Moore, 2007). Placebo controlled trials may not recruit highly representative patients and these rates may be misleadingly supportive of monotherapy success (Licht et al., 1997). A more naturalistic study of the use of olanzapine showed that of 2004 patients, 33.6% were treated with olanzapine as antimanic monotherapy, and 66.4% received olanzapine in combination with other antipsychotics, anticonvulsants, and/or lithium. This European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) observational study showed that clinicians preferred combinations in more severe patients, in rapid cyclers, and in patients who were already on ongoing therapy with mood-stabilising agents; a fourth factor was the country of origin of the psychiatrist (Vieta et al., 2008a). An audit study of treatment in 63 German, Swiss and Austrian hospitals between 1994 and 2004 showed that manic patients were receiving on average of about three medicines each (Wolfsperger et al., 2007). In clinical practice, various antimanic agents such as antipsychotics, lithium or valproate are frequently combined. Such a strategy is used in cases not responding sufficiently to any given first line drug or in severely ill patients where a combination of drugs is believed to be more efficacious than the drugs given as monotherapy. In certain cases the tolerability of two drugs given together in lower doses may also seem to be better that of one of the drugs given in higher doses. The pharmacological reasoning behind combining drugs in mania is imprecise. It is based on the pragmatic assumption that drugs of different mechanism may act additively or synergistically in terms of efficacy. Combinations of an antipsychotic and lithium or valproate may act together to attenuate dopaminergic transmission, but there is no clear hypothesis to explain why.

Combination of an antipsychotic with lithium or valproate is well supported by a number of rather similar trials (Perlis et al., 2006; Sachs and Gardner-Schuster, 2007). Most patients entered in the studies have shown an insufficient acute response to lithium or valproate. However, there is often no

meaningful distinction drawn between subjects responding insufficiently to an acute antimanic treatment with lithium or valproate and subjects suffering from break-through mania during prophylaxis. This limits both the precision with which the treated population has been defined and the extent to which the results can be generalized. The usual run-in with monotherapy requires either lithium or valproate to be prescribed at an optimum level defined by blood testing. In general, the earlier in an initial monotherapy one randomises to combination treatment the more one risks that a response will actually be occurring to the original monotherapy. Therefore a delay increases the validity and power of such studies to demonstrate a true additive effect (if sufficient time is allowed for treatment effects to take place), hence a minimum 2 weeks before randomization.

These combination studies in acute mania were placebo controlled, sometimes with a comparator such as haloperidol, and conducted over 3 weeks. While of short duration, such studies are relevant to the demands of acute mania and are more feasible for being short and allowing limited rescue medication. Drop-out rates tend to be lower than with placebo controlled monotherapy trials. Numbers need to be powered on the expectation of significant response rates in the lithium/valproate + placebo monotherapy arm. Trial design is illustrated in Fig. 1. The comparison with lithium or valproate plus antipsychotic versus lithium or valproate plus placebo has been completed for the following antipsychotics: ariprirazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone (Smith et al., 2007).

Combining an antipsychotic with carbamazepine has not been shown to provide any further advantage in terms of efficacy: negative findings have been published for combination with risperidone (Yatham et al., 2003)and olanzapine (Tohen et al., 2008).

In relation to safety, the available trials indicate that the combinations of an antipsychotic and lithium (or valproate) are acceptable, although the tolerability may be decreased. For example, in the case of lithium and olanzapine, weight gain is likely to be greater than with monotherapy (Torrent et al., 2008).

Most of the trials have demonstrated advantages in the addition of an antipsychotic to lithium or valproate. This includes the atypicals (except for ziprasidone: beneficial only on secondary measures) and haloperidol. Since the patient population is not well defined no claim beyond the acute efficacy already seen in placebo controlled monotherapy trials has been made by companies on the basis of these studies. An additional claim would only be possible if patients were formally demonstrated to be meaningfully refractory/treatment resistant. The trials performed to
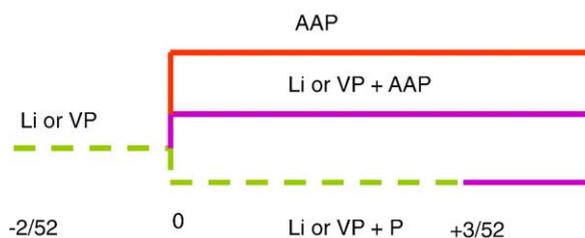
regulatory standard support the addition of either an atypical antipsychotic or haloperidol to lithium or valproate. It is important that there are no additional safety concerns for the short term. US guidelines have proposed de novo combination treatment for all severe manic episodes with an antipsychotic and "mood stabilizer" (American Psychiatric Association, 2002). This also reflected a desire to see mood stabilizers (lithium or valproate) employed in "all phases of treatment". However, only limited data support this strategy except for those patients partially non-responsive to a mood stabilizer alone. A different way of looking at the problem has suggested that valproate could be used to reduce the dose of haloperidol required in acute treatment (Muller-Oerlinghausen et al., 2000).

It was recommended by the meeting that an increased validity for the comparison would be to treat patients with a third arm: the atypical antipsychotic alone (Fig. 1). Such trials would have a number of advantages over existing approaches. If, for example, the antipsychotic alone was comparable to the combination, then this would argue strongly against any additive or synergistic effect of the combination. Further, if the antipsychotic were superior to the active treatment with lithium/valproate plus placebo it would give direct evidence for the superior effect of the new compound (in this case the antipsychotic). In fact, there are no examples yet of three-way trials comparing lithium/ valproate with lithium/valproate plus an antipsychotic and an antipsychotic alone.

The potential disadvantage of this design would be the acute withdrawal of lithium or vaproate and any effects this might have on current manic symptoms. This would, nevertheless, be informative for the clinical validity of seeking an augmentation effect from combination. If most of the patients were to receive the combination de novo, this design would address the question of whether always to combine an antipsychotic with valproate (or lithium) in severely ill patients. Finally, the powering of a 3-arm design would require careful consideration of the primary trial question. Since this would likely be the superiority of combination over lithium or valproate monotherapy, for which there is abundant existing data to guide patient numbers, the monotherapy antipsychotic arm would probably provide exploratory secondary comparisons with the other arms and should be powered accordingly.

Valproate would be expected to have effects on the metabolism of antipsychotics that might increase their effective levels. Blood levels at the termination of combination trials would provide helpful additional information.

Finally, if the antipsychotic in monotherapy were superior to lithium/valproate the demonstration of efficacy against placebo in the presence of another drug seems, in principle, to demonstrate that such designs could be useful in the evaluation of new treatments. If this design makes studies appreciably more feasible, such combination trials could lead and support monotherapy trials.

There is no controlled data on combining antipsychotics in mania.

## 6. Long term combinations in bipolar disorder

The use of combinations of antipsychotics with other drugs is very common in routine long-term treatment of bipolar



**Figure 1** Treatment of acute mania showing partial response to lithium or valproate monotherapy.

disorder. However, data supporting this practice are still limited. Several antipsychotics have now been studied in combination with lithium or valproate in relapse-prevention trials. An olanzapine study supported prevention of mania on secondary outcomes but was underpowered; ziprasidone showed efficacy against the primary outcome of relapse to any episodes; quetiapine showed enhanced prevention of all mood events and, indeed, manic events and depressive events separately (Tohen et al., 2004; Vieta et al., 2008b; Suppes et al., 2009). These samples were selected on the basis of an acute response to the atypical antipsychotic and many of these patients may have prior insufficient prophylactic response to lithium or valproate.

The rationale for this sort of combination is that antipsychotics, lithium, and valproate have different and potentially complementary mechanisms of action. Potential pharmacokinetic interactions may play a role in acute treatment, but proved to be minimal in the long term. The design of the trials so far has been to start with open combination treatment and to randomize responders to stay on combination or to shift to mood stabilizer plus placebo. The use of these combinations will be limited by adverse effects (see below), but could be justified in patients refractory to other treatments. Indeed, the majority of patients in the trials mentioned are presumably refractory to valproate or lithium. Additionally the long term use of antipsychotics for this indication could be justified in patients not achieving full remission, more severely ill psychotic patients, and special populations such as patients with mixed states, and rapid cycling.

Outcomes in relapse prevention studies remain pragmatic. The most sensitive outcome measure in bipolar studies is probably time to intervention for a new mood episode, first used in the lamotrigine monotherapy relapse-prevention studies. This is a clinically meaningful endpoint but others such as remission or functional recovery might be more attractive to patients. While attrition rates in very demanding studies limit statistical power, sensitivity remains the most relevant issues in long-term trials. Alternative measures of chronic sub-syndromal symptoms or functional outcome merit investigation.

## 7. Major depression

The overall efficacy of all available antidepressants when used as monotherapy to treat major depressive disorder (MDD) is, at best, modest. For example, a meta-analysis (Papakostas and Fava, 2009) of all double-blind placebo-controlled studies of antidepressants published since 1980 revealed response rates of 53.8% for antidepressants versus 37.3% for placebo (difference in response rate of 16.5%). A recent analysis of all the trials, published and unpublished submitted to the European authorities showed a similar magnitude of effect, with little evidence for much impact of baseline illness severity, despite selective claims to the contrary (Melander et al., 2008). The STAR*D treatment study showed an average response rate of 47% and remission rates of around 30% for patients treated with citalopram in a variety of outpatient settings (Trivedi et al., 2006).

There is clearly a challenge when conducting placebo controlled trials in representative clinical samples with significant depressive illness, but all the published findings suggest that first line treatments commonly fail for reasons of efficacy or tolerability and this results in a significant proportion of patients who require 2nd, 3rd, even 4th-line treatment in order to achieve full remission of symptoms. The consequences of untreated or chronic persisting depression are profound. Augmentation with atypical antipsychotics has been suggested to be beneficial in this indication.

The focus of depression trials has been an augmentation claim that can be based on a defined patient population. This has required an adequate definition of antidepressant treatment resistance. The usual trial design is for patients to first receive open-label antidepressant monotherapy for 6–8 weeks. The patients who, at the conclusion of the open-label trial, do not meet a pre-defined criterion of sufficient improvement (usually clinical response) continue on the same dose of their antidepressant as in the open-label phase and are typically randomized either to the addition of placebo or an antipsychotic (Fig. 2). Studies have been conducted with a number of different atypical antipsychotics. A meta-analysis of the first ten randomised controlled trials conducted (including a total of 1500 patients) (Papakostas et al., 2007) showed that increased rates of remission were typical in this trial design. The remission rate for atypical antipsychotics were 47.5%, and for placebo 22.3%. The effect size therefore represents an absolute increase in response of 25% or a number needed to treat of only 4. However in this particular case there was a significant almost equal difference in the rate of drop out for adverse effects.

Because the indication for antidepressant treatment in many severely depressed or refractory patients is long-term, appropriately extended evidence on efficacy and safety would be desirable. The minimum might be a simple extension of treatment over the long term, but withdrawal of an augmenting antipsychotic in a relapse prevention design would also be informative. Unfortunately, the only long-term, placebo-controlled trial of an atypical antipsychotic as augmentation for MDD conducted to date did not show differential relapse rates among citalopram–risperidone remitters who either continued therapy with combination therapy versus citalopram monotherapy (Rapaport et al., 2006). Relapse rates after augmentation with risperidone were high and similar in risperidone and placebo arms suggesting possibly only a short term benefit. Relapse prevention studies to clarify the need for long term combination treatment are desirable, since unnecessary continuation of an antipsychotic, given the attendant potential adverse effects, is not desirable. Relapse prevention studies require careful recruitment of a defined refractory population, treatment to
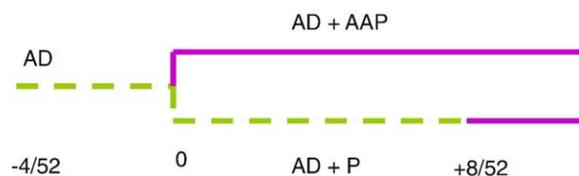


**Figure 2** Treatment of major depression showing refractory response to antidepressant monotherapy.

remission and randomization to continue or discontinuation (with appropriate taper) of the augmenting agent.

## 8. Schizophrenia

The use of more than one antipsychotic in schizophrenia is surprisingly common. Estimates from the United States suggest that 33% of patients may receive two antipsychotics and almost 10% receive three (Correll, 2008). Co-prescription of other drugs is also common. US schizophrenia experts recommended various augmentation strategies in partial but inadequate response (adding a long-acting injectable atypical antipsychotic, valproate, an oral atypical antipsychotic etc), but all these possibilities were considered "second-line" due to the limited evidence available (Kane et al., 2003). The same phenomenon of combining antipsychotics in around 20% of patients with schizophrenia is evident in European studies (De Hert et al., 2006b; Edlinger et al., 2005; Rittmannsberger et al., 1999). A particular problem in in-patient services appears to be the addition of optional doses or combinations "as required" (Paton et al., 2008). Thus, antipsychotics tend to be combined too early in acute treatment, before adequate response can be established. The widespread nature of the prescribing practice contrasts unfavourably with the meagre evidence base to support it. This is probably more discrepant than for any other indication for the use of antipsychotics in combination described here.

Given that, as noted, the common action of antipsychotics is dopamine blockade, it is particularly challenging that clozapine blocks only 30−50% of the D2/3 receptors; yet clozapine is also apparently the most effective existing antipsychotic (Kane, 2008). This finding suggests a priori that combinations of antipsychotics may often be pointless. However, augmentation of clozapine's action is of genuine interest, and has attracted the most current interest.

Where clozapine has had only limited benefit as monotherapy, it may be logical to add a drug with higher D2/3 potency so as to increase dopamine receptor blockade. To take specific published examples, a small study of non- or partial treatment responders to clozapine, showed that the addition of sulpiride was superior to placebo (Shiloh et al., 1997). When risperidone was added to clozapine in a similar design this also showed a modest difference in the clozapine plus risperidone group in terms of BPRS total symptoms (Josiassen et al., 2005). Another randomized-controlled trial addressing the same question but showing no effect, was published in a high impact journal (Honer et al., 2006). All of these studies have at least one problem in common—they are small or modest in size—and hence variation in outcome would be predicted. Despite the published negative findings, publication bias will tend to favour positive findings.

In a systematic review of 19 randomised, almost all double blind studies with 1214 participants, mean age 33 years and mean trial duration of 12 weeks (Correll et al., 2009), the pooled odds ratio suggested a small effect favouring combination treatment, both in terms of defined response for each study and in the total numbers of drop outs for any reason, where this could be calculated. Thus, while the balance of effect is positive, the results were highly heterogeneous, which is not entirely surprising since different combinations were included with rather different strategies and the studies were individually small. There was also a positive publication bias. Positive effects appear to have been associated with studies in which combinations were started from the beginning of treatment (not after establishing refractoriness), clozapine combinations (not other antipsychotics), trial durations greater than 10 weeks (confirming other analyses (Paton et al., 2007) and studies conducted in China (where clozapine is a first line treatment). Another systematic review limited consideration to combinations with clozapine in (partial) non-responders and found little effect (Brambilla et al., 2002). Overall, the evidence is inconclusive and well-designed studies would require better defined patient populations, plus larger and longer trials.

Adding antiepileptic drugs to antipsychotics is a popular treatment option although the evidence to support it is meagre. In a review of studies adding valproate to antipsychotics it was concluded that this should be a last resort management strategy (Basan et al., 2004).

Experience with combinations of other medications might be of interest for purely pragmatic reasons, but other combinations are essentially experiments in polypharmacy. In defining an improved basis for practice there is a need for 1) larger studies, 2) a clearer definition of the sample population (existing studies have sometimes taken patients at the beginning of an acute episode, in others, non-response had been established). Established non-response is probably the most appropriate focus. 3) A clear dosing strategy.

A possible design is shown in Fig. 3. This supposes that patients enter after one retrospective plus one prospective treatment failure on a single index antipsychotic (e.g. risperidone). Entry to the study would also require a high PANSS, and little response to risperidone over 4 weeks. Randomization would then be to continue risperidone plus placebo, add the potentially augmenting drug to rsiperidone or switch to clozapine. Clozapine would provide the key validating comparison for the combination as the most effective monotherapy. Appropriate matched blood monitoring would be required in each arm.

In summary, combinations appear to be widely favoured by clinicians, and we may assume are usually associated with acceptable clinical outcomes in schizophrenia. However, better evidence on this point would be very desirable, especially because combinations may often produce more side effects. Moreover, despite some positive data, there is currently no biological or evidence based rationale why combinations should be superior to monotherapy. Combinations of antipsychotics with high affinity for D2/3 blocking may often be pointless.
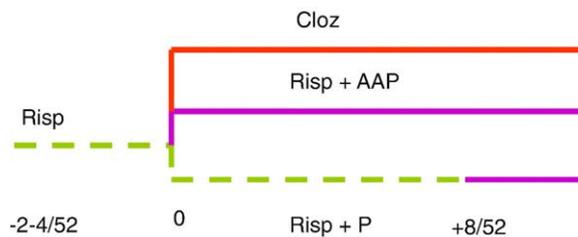


**Figure 3** Treatment of acute schizophrenia showing non-response to prospective risperidone monotherapy (and retrospective non-response to a second agent).

# 9. Obsessive—compulsive disorder (OCD)

OCD is a chronic illness involving either obsessions or compulsions that cause marked distress, occupy more than 1 h a day and significantly interfere with normal routine and occupational or social functioning. The symptoms are recognised by the patient as excessive or unreasonable but the recognition that an obsession is always senseless is not an essential characteristic of an obsession.

Polypharmacy is often a feature of OCD as of other severe psychiatric disorders. Even among young people treated in clinical samples, about 50% received more than a single medicine. However, OCD is relatively under-diagnosed and hence under- rather than over-treated in population terms (Hollander, 2007) and a potentially larger number of patients may require treatment than are currently known to psychiatric services or general practitioners. Diagnosis is desirable because there are useful treatments in both psychological and pharmacological modalities. There is good evidence for pharmacological efficacy of drugs inhibiting the reuptake of serotonin such as clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram. Moreover, completion rates in OCD trials are unusually high, compared with other psychiatric disorders (Khan et al., 2007) However it is widely conceded that response is often only partial and often unsatisfactory.

Antipsychotics can be considered as combination therapy (with drugs inhibiting the reuptake of serotonin) in four situations in OCD. 1) OCD with poor insight ("psychotic features"), 2) refractory OCD, 3) OCD with tick and 4) when there is co-morbidity, for example between schizophrenia and OCD. Indications 1—3 merit careful discussion. Example 4 will not be considered further. The use of combinations in OCD treatment is a common practice now supported, at least partially, by formal short term trials for OCD with tic and refractory OCD, but it has not been thoroughly examined for OCD with poor insight.

The disorder represents a psychopathological spectrum with a varying continuum of insight. In the case of psychotic features occurring in obsessive compulsive disorder, obsessional delusions do not necessarily signify a schizophrenia diagnosis. In other words OCD with psychotic features is a severe form of OCD and not a form of schizophrenia. However, lack of insight may underlie a clinically meaningful sub-classification and could indicate the need for antipsychotic augmentation. The DSM-IV approach is to specify patients to have poor insight type if, for most of the time during a current episode, the person does not recognise that the obsessions and compulsions are excessive or unreasonable. Insight as a predictor of treatment response has not been explored adequately and the apparent logic of augmentation with antipsychotic medication requires further investigation in patients with psychotic features. However, as it stands now, and based on the study of (Eisen et al., 2001), the initial approach should be with medium to high dose of SSRI, and only in refractory cases, is augmentation with antipsychotics warranted.

Refractory OCD has been found to respond to augmentation of an SSRI with an antipsychotic Definition of refractoriness requires 3 months of maximal monotherapy treatment with a SSRI. One-third of refractory patients responded favourably to augmentation with antipsychotics (response was

defined as a decrease of at least 35% in Y-BOCS score) (Bloch et al., 2006). There is positive evidence for risperidone, haloperidol, olanzapine and quetiapine (although a recently published study found no difference between quetiapine or placebo augmentation to SSRI therapy in treatment-resistant OCD (Kordon et al., 2008). In practice, no response within a month usually means that the augmentation will not work, so augmentation trials should last at least 4 weeks, but preferably longer. The apparently greater effectiveness of haloperidol and risperidone raises the hypothesis that greater dopamine receptor affinity may be what is required in treating refractory OCD but currently there is no decisive experiment to decide that observation.

The sub-group of OCD with tic may have a relatively higher responsiveness than those without (Bloch et al., 2006). Hence, for this subset of patients, combination therapy might be considered as treatment of choice.

Given the moderate overall average benefit of SSRI monotherapy, there is interest in a combination strategy from the start of treatment in severe OCD. Recent unpublished data from143 patients with OCD previously largely untreated, compared those randomized to start either the combination of quetiapine and citalopram or citalopram plus placebo (Vulink et al., 2007). Promising short term benefits were noted with the combination and the need for a long term strategy based on combination of treatments requires further supporting evidence. The safety issues will be covered below but are raised by the introduction of antipsychotics into a new population. Longer term data with better evidence for functional improvement and the addressing of safety concerns is required.

# 10. Antipsychotics and adverse effects in severe mental illness

Cardio-metabolic risk in patients with severe mental illness and especially when treated with antipsychotic agents are a growing clinical concern (Bobes et al., 2007; Fleischhacker and Kahn, 2008). People with severe mental illness are at risk to die prematurely, mainly due to cardiovascular disease, and recent studies indicate that this risk has been increasing over the last decades. Over recent years evidence has accumulated suggesting that a number of antipsychotics negatively influence cardiovascular risk factors and can induce hyperglycaemia and diabetes (Fraguas et al., 2008).

Most studies evaluating metabolic and cardiovascular side-effects of antipsychotic medication have been performed in patients on monotherapy. However, it would seem logical to assume that combining antipsychotic agents with a high metabolic risk would lead to increased metabolic abnormalities and naturalistic data support this prediction (Citrome et al., 2004). On the other hand, there is some preliminary evidence that adding aripiprazole, which has a mostly weight neutral profile, to clozapine may reduce clozapine induced metabolic side effects (Fleischhacker et al., 2008; Fleischhacker and Kahn, 2008; Henderson et al., 2006). There may be multiple factors at work mediating the effects of the antipsychotics, which confound the effects of polypharmacy (Correll et al., 2007). One is clearly accumulated weight gain. Another may relate more directly to the actions of dopamine antagonists on glucose homeostasis, perhaps via dopamine terminals in the hypothalamus. Thus, the dopamine

agonist bromocriptine has been shown to be an effective anti-diabetic agent, even in patients refractory to conventional oral hypoglycaemic agents(Cincotta et al., 2008; Scranton et al., 2008).

There is some data suggesting that polypharmacy is associated with higher use of somatic co-medication in general. Thus, combination studies should include relevant screening methods, which are well established for the general population.

There is a small and growing literature on strategies to manage metabolic risk in patients treated with antipsychotics. Add-on strategies have been explored to prevent weight gain and other metabolic abnormalities with different agents in mainly small studies. When patients on antipsychotics develop diabetes, hypertension or severe dyslipidemia the treatments used in the general population for these illnesses appear equally effective in patients with schizophrenia (De Hert et al., 2006a), but this will lead to more complex medication regimes.

The propensity of antipsychotic agents to cause hyper-prolactinaemia is related to their potency in antagonising D2 receptors in the anterior pituitary and not to their propensity to motor side effects. Thus the atypicals, sulpiride and ami-sulpiride both elevate prolactin. Since pituitary receptors are effectively outside the blood-brain barrier, their blockade may be particularly extensive by those drugs that require relatively high circulating levels for adequate brain penetration (e.g. risperidone). Others among the newer atypical antipsychotics (of which clozapine is the prototype), have a relatively poor affinity for D2 receptors and do not elevate prolactin significantly (e.g. quetiapine, olanzapine).

The clinical relevance of hyperprolactinaemia is still debated in the field. The conventional view is that a mere elevation of prolactin plasma levels, if an organic cause like prolactinoma has been ruled out, is of no major concern in the absence of clinical symptoms (Hummer and Huber, 2004). Adverse events such as gynecomastia, menstrual irregularities or sexual dysfunctions may be linked to hyperprolactinaemia and warrant interventions which may range from watchful waiting to dose reduction or ultimately a switch of medications. On the other hand, hyperprolactinaemia may have been underestimated as a cause of long term side effects. It is possible that hyperprolactinaemia causes suppression of the reproductive endocrine axis and consequent bone mineral density (BMD) loss. There are high rates of osteoporosis and osteopenia in those taking long-term antipsychotic drugs (Hummer et al., 2005) and this may is related to the dose and duration of treatment, although confounded by other risk factors in this patient group. Bone loss is associated with hypogonadism in male (Kishimoto et al., 2008)and female groups, but young Caucasian women appear to be particularly vulnerable to developing hyperprolactinaemia and the associated hypogonadism and bone loss (Meaney and O'Keane, 2007). The occurrence of menstrual dysfunction should alert clinical suspicions of hyperprolactinaemia and bone de-mineralisation. There are no published trials examining the effects of hormone replacement on BMD in those taking long term antipsychotic drugs but it would be expected that this could halt or even reverse the process. Larger, longer term prospective trials are badly needed here.

Combination treatment, e.g. adding aripiprazole (a partial agonst at D2 receptors), has been reported to attenuate or abolish hyperprolactinaemia in antipsychotic treated patients (Shim et al., 2007). This is an unusual example of where combination treatment may serve to reverse unwanted adverse effects of another antipsychotic.

Tardive dyskinesia (TD) remains a potential risk for patients treated long term with antipsychotics (Keck et al., 2000). Since acute EPS are still regarded as a predictor of subsequent TD, the lower EPS burden associated with the use of the atypical antipsychotics (Leucht et al., 2009) and the use of the typical drugs at lower doses should reduce the long term risk. Current data on TD with atypical antipsychotics support but do not prove reduced risks with the atypical agents (Correll and Schenk, 2008). The use of anticholinergic drugs to reduce the burden of extra-pyramidal side effects is most marked with high potency classical antipsychotics (De Hert et al., 2007).

Combinations of antipsychotics with other drugs or with other antipsychotics may also carry greater risk of neurocognitive side-effects (Frangou et al., 2005).

There is a general problem that the long term complications of medicines used to treat all relevant disorder are poorly distinguished in terms of particular risks attributable to combinations.

## 11. Conclusions

Combination treatment involving an antipsychotic, is common in clinical practice in psychiatry. Its basis may be entirely pragmatic, yet well supported by the evidence as in mania, bipolar maintenance, refractory depression or OCD, or more logical yet poorly supported by existing data as in the addition of antipsychotics to clozapine in schizophrenia. The fundamental requirements for improved practice include better characterised patient groups (usually defined by treatment non-response), larger studies, longer observation times and more attention to safety/physical health concerns. Claims for additional efficacy to regulatory bodies need to recognize these factors. The key indication is likely to be augmentation in refractory patients and possibly the need for combination treatments de novo in some patient populations such as OCD.

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