



History, background, concepts and current use of comedication and polypharmacy in psychiatry

H.-J. Möller¹, F. Seemüller¹, R. Schennach-Wolff¹, S. Stübner², E. Rüter¹
and R. Grohmann¹

¹ Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Nussbaumstr.7, 80336 Munich, Germany

² Bezirkskrankenhaus Augsburg, Dr-Mack-Straße 1, 86156 Augsburg

Abstract

Based on a careful literature search a review is presented of the history, background, concepts and current use of comedication and polypharmacy in psychiatry. The pros and cons of comedication and polypharmacy are presented, as well as their apparent increase in recent times. Possible reasons for the increase of comedication/polypharmacy are described. Both the potential advantages as well as the potential risks are discussed. The one sided view that all comedication/polypharmacy is nothing but problematic is questioned. Comedication/polypharmacy seems to be, among others, the current answer to the well-known limited efficacy and effectiveness of current monotherapy treatment strategies.

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Introduction

With the invention of antipsychotic, antidepressive, tranquilizing and mood stabilizing medications in the 1950s, psychopharmacological treatment became one of the main treatment approaches in psychiatry, if not the most important. This was, in principle, a success story, but several limitations, such as delayed onset of efficacy, unsatisfactory efficacy, tolerability problems, and so on. were also observed. In the last 20 to 30 years second generation antipsychotics (SGAs) and antidepressants have entered the market, developed to overcome some of these problems. However, the progress made is primarily related to better tolerability rather than efficacy. There are still several unmet needs which can hopefully be reduced significantly in psychopharmacological treatments in the near future (Tandon et al., 2008; Möller, 2010, 2011, 2012).

Along with the development of new/better and more specific compounds, comedication/polypharmacy has been, and is still, a widely used strategy to

overcome the limitations of monotherapy with the currently available psychotropic drugs. This paper aims to describe the background and history as well as the concepts and the current status of comedication/polypharmacy, focusing on the field of schizophrenia and depression. Generally speaking, comedication/polypharmacy is a very common phenomenon for different reasons, and is difficult to reduce (Stahl, 1999a, b; Viola et al., 2004; Biancosino et al., 2005; Barbui et al., 2006; Russell et al., 2006; Megna et al., 2007; Pandurangi and Dalkilic, 2008; Thompson et al., 2008; Alda and Yatham, 2009; Glezer et al., 2009; Goldberg et al., 2009; McIntyre and Jerrell, 2009; Mistler et al., 2009; Shelton et al., 2010).

Limitations of drug treatment in schizophrenia and depression as one possible background for comedication/polypharmacy

In general, medicine polypharmacy, e.g. in the treatment of hypertension, of diabetes or in the antibiotic treatment of infections, has nowadays become more a rule than an exception. Antibiotic combination regimens, for example, with different specific modes of action, are often chosen to cover a spectrum of different pathogens at once, or to manage drug resistant bacteria. The ideal equivalent approach in psychiatry would be to target specific symptom clusters or

Address for correspondence: Professor H.-J. Möller, Department of Psychiatry, Ludwig-Maximilians-University München, Nussbaumstrasse 7, 80336 Munich, Germany.
Tel.: +49 89 5160 5501 Fax: +49 89 5160 5528
Email: hans-juergen.moeller@med.uni-muenchen.de

comorbidities by combining psychopharmacologic drugs specifically targeting the underlying key neurotransmitters. Unfortunately, the situation in psychiatry is more complex, as syndromes and symptoms cannot easily be reduced to single neurotransmitters. On the other side, the development of biological psychiatric illness concepts, with the consideration of specific neurotransmitters, went hand in hand with the development of the first psychotropic drugs.

Since the development of chlorpromazine, antipsychotics have formed the basis of schizophrenia treatment for more than 50 years (Möller, 2010). In terms of their chemical structure, antipsychotics, traditionally called neuroleptics, are a heterogeneous group of **psychoactive** drugs and include phenothiazines, thioxanthenes, butyrophenones, diphenylbutylpiperidines, benzamides, benzisoxazoles and dibenzepines (Möller, 2012). They are used in acute phase treatment as well as for long-term treatment and prevention of relapses (Falkai et al., 2005, 2006).

Based on the clinical efficacy of neuroleptics, the dopamine hypothesis was developed. It implies that in patients with schizophrenia there is an increased production of this neurotransmitter (Schmitt et al., 2008) or an over-sensitivity of dopamine receptors in certain brain regions (especially the mesolimbic system) resulting in the appearance of positive symptoms, along with a hypodopaminergic state in frontal brain regions associated with negative symptoms (Sedvall and Farde, 1995). The hypothesis of a hyperdopaminergic state is supported by the successful treatment of psychotic symptoms by neuroleptics which are antagonists of D2 receptors. Besides dopamine, other neurotransmitters, like serotonin (5-HT) and glutamate, seem to be involved in the pathophysiology of schizophrenia (Möller, 2008c). The blockade of 5-HT_{2A} receptors and the preferential blockade of specific subtypes of dopamine receptors was hypothesized to be a relevant mechanism for treating negative symptoms (Möller, 2003), especially in the development of SGAs in the last two decades.

Although SGAs represent an important progress in the medication of schizophrenia, especially concerning lower EPS liabilities, and to a lesser degree concerning superior efficacy and a broader spectrum of efficacy, the latter results have in no way fulfilled the expectations which were primarily associated with the advent of the SGAs (Tandon et al., 2008). Another problem is that at least some of the SGAs induce weight gain to a remarkable degree, and this is associated with metabolic risks (De Hert et al., 2009). Clozapine still seems to be the best representative of the SGAs in various aspects, especially regarding the efficacy in

refractory patients, but it is also associated with high risk of weight gain and lower risk of agranulocytosis, with a possibly fatal outcome. Thus, there is still an urgent need to solve the unmet needs of current drug treatments for schizophrenia. This includes the following: better efficacy for negative symptoms, better efficacy for cognitive disturbances, better efficacy for depressive symptoms, better efficacy in refractory patients, no weight gain or associated metabolic issues, excellent general tolerability and safety, an improved acceptance by patients and an increased subjective well-being/quality of life.

The development of the SGAs and their claim for a broader clinical efficacy (Agid et al., 2008) was based on the concept that the multiple symptom domains of schizophrenia could be effectively treated with a single agent, demonstrating heterogeneous pharmacological intervention in the sense of 'intra molecular polypharmacy' (Kim et al., 2009). However, more and more evidence arises that, at least at present, this concept is difficult to realize with the currently available compounds. Instead, there is increasing support for the notion of possibly using multiple compounds, each for a specific syndrome. In the line of this thinking it is interesting that the American drug authority, the FDA, has, for the first time, endorsed the possibility of approving drugs that might be used in conjunction with antipsychotics, if a clear efficacy in the treatment of special syndrome domains, such as negative or cognitive symptoms, can be demonstrated (Laughren and Levin, 2006). It is still assumed to be possible that different symptom domains within schizophrenia can be mediated through a common pathophysiological mechanism, supporting the position that a non-selective intervention with compounds targeting multiple receptors can translate to broad clinical improvement. Alternatively, and in line with the mentioned shift in drug development, schizophrenia may well represent a collection of different pathophysiological mechanisms, and optimal treatment in the future will probably include different agents, each uniquely targeting a specific dimension of schizophrenia, with treatment tailored for the individual patient (Kapur and Mamo, 2003). Current drug developments for antipsychotics are going in the direction of multi-receptor compounds involving the dopaminergic and serotonergic system in searching for new frontiers, with special focus on the glutamatergic system (Arranz and Kerwin, 2003; Miyamoto et al., 2005; Arranz and de Leon, 2007; Möller, 2010). Positive study results in treatment-resistant schizophrenia patients for clozapine augmentation with glutamatergic substances such as lamotrigine and CX516 seem to give support

to this hypothesis (Sommer et al., 2012). These reflections on the present situation and the future of medication to treat schizophrenia are necessary to understand the basis for some demands in this field, and possible ways to answer these with an 'intra molecular polypharmacy' or by combining two or more compounds (Kim et al., 2009). The field of schizophrenic medication is chosen here as an example. These principal thoughts can easily be extended to other areas as well.

In terms of depression medication, imipramine, the first antidepressant, as well as several other traditional tricyclic antidepressants, such as amitriptyline and doxepin, have a broad spectrum of pharmacological properties: apart from reuptake inhibition of serotonin and noradrenalin they also have receptor blocking properties, e.g. on the muscarinic and histaminergic receptors. These latter might be primarily side effect related, but they might also contribute to the clinical efficacy profile in the sense of 'intra molecular polypharmacy' mentioned above (Kim et al., 2009). Since the development of imipramine more than 50 years ago, antidepressants have been seen as standard treatment for patients suffering from depression (Möller, 2010). Related to current diagnostic categories of depression, 'major depression' (DSM IV) or 'depressive episode' (ICD 10) are the main indications for treatment with antidepressants, especially those of moderate or severe intensity (Möller et al., 2011). Depression is explained by a complex aetiopathogenesis involving, among other things, genetic dispositions and psychosocial stressors as well as alterations of the serotonergic, noradrenergic and dopaminergic transmitter systems. Dysthymia and depressive adjustment disorders, primarily related to psychosocial stress factors in early life or in the current life situation, do not respond as well to antidepressive compounds (Möller, 2009a; Rush et al., 2009). The monoamine-oxidase (MAO) inhibitors seem to have special indication in atypical depression (Henkel et al., 2006).

The efficacy of the traditional antidepressants (ADs) (mostly tricyclics) and modern antidepressants (mostly SSRIs and SNRIs) is well proven. However, the efficacy of modern ADs has been criticised as too low regarding clinical relevance by some authors (Kirsch et al., 2008), a criticism that can be rejected when carefully reviewing all data (Möller, 2008b; Fountoulakis and Möller, 2011). Nevertheless, the pre-post-differences between antidepressant treatment and placebo is only in the range of 2–3 points in the Hamilton Depression Rating Scale (HAM-D) and the placebo-verum differences of response rates are only in the range of 15–20%, depending on the type of

antidepressant, severity of depression, etc. (Möller, 2008a), suggesting that future compounds with greater efficacy are needed. Compared to the pharmacological mechanisms of the first and second generation of antidepressants, the recently licensed antidepressant agomelatine can be judged to be an innovative approach: a melatonin MT1 and MT2 agonist and a 5-HT_{2c} antagonist with a special focus on sleep and circadian rhythm disorder which are a relevant subcomponent of depressive symptoms (Eser et al., 2007; Kasper et al., 2010; Kennedy and Rizvi, 2010).

Just as in the field of drug treatment of schizophrenia, there are also still serious unmet needs in the treatment of depression, despite the introduction of the selective serotonin reuptake inhibitors (SSRIs) and other modern antidepressants, including also the recently introduced agomelatine, which has improved some aspects of depression treatment, predominantly in terms of side effects. The most relevant unmet needs in the treatment of patients with depression are delayed onset of response, limitations in the effectiveness, limitations in achieving remission, an unsatisfactory high proportion of poor responders/non-responders and tolerability issues, depending on the class of antidepressants. Thus, there are still good reasons for further drug development in this field, which lead in different directions. Some are based on the traditional transmitter hypothesis; others are focusing on new targets such as interventions on the stress hormone axis, the neurokinin system or the glutamatergic system (Schechter et al., 2005; Norman and Burrows, 2007; Millan, 2009). It seems that so far efforts have been made to overcome some of the described clinical treatment problems by comedication/polypharmacy.

General aspects and concepts of comedication/polypharmacy

The terms comedication and polypharmacy are not well defined and are used in somewhat different ways, hampering a consensus understanding of the approaches. According to Preskorn and Lacey (2007) clinicians use polypharmacy for several reasons:

1. To treat two pathophysiologically distinct but comorbid illnesses in the same patient;
2. To treat the same condition or two 'comorbid' syndromes (e.g. major depression plus panic disorder) in the same patient;
3. To increase the efficacy of the primary treatment by e.g. combining a selective serotonin reuptake inhibitor (SSRI) with another antidepressant like

Table 1. What drives clinicians to comedication/polypharmacy?

<ul style="list-style-type: none"> * Delayed onset of action * Limited efficacy in terms of pre-post score changes * Insufficient drug effect (in terms of response/remission) * Insufficient drug response in terms of special syndromes of a complex symptomatology, e.g. sleep disturbances or anxiety in depression, depressive or negative symptoms in schizophrenia * Non-response, treatment resistance * Irrational expectations of treatment outcome * Comorbidities * 'Antidotes' against side effects
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e.g. mirtazapine to treat a patient with major depression;

4. To provide acute amelioration while awaiting the delayed effect of another medication, e.g. using lorazepam in acute mania while waiting for the anti-manic effects of a mood stabilizer;
5. To treat intervening acute phases of an illness, e.g. adding an antidepressant to a mood stabilizer when a bipolar patient develops a depressive episode;
6. To treat adverse events produced by the primary drug, e.g. adding an anticholinergic when a patient develops dystonia on a neuroleptic;
7. To switch medication from one compound to another with a limited overlapping time.

Comedication is often used in the sense of combining two medications with the same indication, e.g. two antidepressants or two antipsychotics. A special type of comedication, the combined treatment of a medication for a given indication (e.g. antidepressant) with a compound with another indication (e.g. antipsychotic) to increase efficacy, is often called augmentation. In most cases comedication strategies are performed to increase efficacy in general, to improve efficacy in a certain subdomain (e.g. negative symptoms in schizophrenia) or to reduce side-effects (Table 1). From a clinical viewpoint this seems rational under certain conditions, e.g. at least some proof of efficacy for the comedication strategy and no unacceptable side effect burden (Preskorn and Lacey, 2007). In this sense several guidelines describe some comedications as meaningful, especially to overcome treatment resistance (Falkai et al., 2005, 2006; Bauer et al., 2007). Especially in the acute and long-term treatment of bipolar disorder (Grunze et al., 2002, 2004, 2010) not only dual but, under certain conditions, even triple combinations are described as indicated: e.g.

combination of an antidepressant and a mood stabilizer in the treatment of acute bipolar depression, and the combination of, if necessary, up to three mood stabilizers in the maintenance therapy of bipolar disorder.

Generally, the questions arise as to where polypharmacy starts; how many compounds need to be applied to declare the respective treatment regime as 'polypharmacy'. This has not been defined so far in a consistent way. Some authors suggest that the combination of three or more medications for the same indication should be called 'polypharmacy'. While comedications under the above described conditions still have some rationality, polypharmacy already seems to have a bad reputation in terms of irrationality, harmfulness, etc., even though in a given case it might be meaningful to combine different compounds to achieve greater efficacy (Stahl, 1999a).

An even more frequent problem than the general question of the usefulness and advantage of comedication and polypharmacy is their use and application in patients who suffer from not one mental disorder, but a combination of mental disorders or a combination of mental disorders and somatic disorders, such as metabolic disorders, vascular disorders, etc. If each of these conditions is treated with one medication, this is, of course, fully rational. Nevertheless it can lead to an increased side effect burden, to compliance problems due to complicated regimens of different medications at different times and to problems of pharmacodynamic and pharmacokinetic interactions, especially related to enzyme induction and inhibition, which should be carefully taken into account by the treating doctor. This might become especially problematic in elderly patients with much comorbidity. In these patients multiple doctors often prescribe medications without considering the full potential of drug interactions.

Rationality/irrationality of comedication/polypharmacy

Especially in the light of evidence-based medicine (Gören et al., 2008; Möller and Maier, 2010), the key criterion for rationality of comedication (Preskorn and Lacey, 2007) is that results from adequate clinical trials are able to prove superior efficacy (Tables 2 and 3). Relevant clinical data on the advantage of comedication is available for only few combination regimes, e.g. lithium augmentation, thyroxine augmentation or augmentation with antipsychotics in the treatment of refractory depression (Crossley and Bauer, 2007; Nelson and Papakostas, 2009) and also for some

Table 2. Principle aspects for rationality/irrationality of comedication/polypharmacy (CM/PP)

✗	Proven/unproven superior efficacy of CM/PP in terms of EBM
✗	Proven/unproven superior efficacy of CM/PP in terms of clinical experience
✗	Pharmacological plausibility/implausibility of CM/PP <ul style="list-style-type: none"> ▶ Positive example: Combination of a weak D2 blocker with a strong D2 blocker
✗	Consideration/non-consideration of pharmacokinetic and/or pharmacodynamic problems of CM/PP <ul style="list-style-type: none"> ▶ Negative example: The combination leads to reduced plasma levels of the first-rank drug treatment
✗	Non-detection of non-compliance or too low plasma levels as reason for CM/PP

other conditions such as resistant schizophrenia (Honer et al., 2006; Suzuki et al., 2008).

Sometimes the data that is available shows neither an improvement nor a worsening of the clinical condition (Glick et al., 2006; Adan-Manes and Garcia-Parajua, 2009). This might be 'real' or due only to insufficient statistical power in the respective trials (Möller and Maier, 2010). For other conditions data are more or less lacking and doctors rely more on their own clinical experience than on the results of clinical trials (Möller et al., 2004; Blier et al., 2010). For example, and against all expectations, comedication with an antidepressant in patients with schizophrenia additionally suffering from a depressive syndrome is far from proven (Whitehead et al., 2002). Examples are naturalistic studies reporting that patients suffering from depressive symptoms were intuitively treated with significantly more antidepressant compounds which, nevertheless, did not keep these patients from suffering a worse course of illness due to greater illness severity.

Generally, it needs to be critically discussed whether or not clinicians can base their decision in terms of polypharmacy on theoretical assumptions of a possible advantage or on some positive clinical experience, or if the use of polypharmacy is only justified by evidence-based medicine. For example, what about plausible theoretical arguments, e.g. the combination of a weak D2 receptor antagonist such as quetiapine with a strong D2 receptor antagonist (like risperidone) in refractory acute psychotic patients, which nonetheless lacks empirical data? Is evidence-based medicine possibly going too far with its demands, destroying the positive impact of theoretical considerations and clinical experiences (Möller, 2009b; Möller and Maier, 2010)? Some of these suggestions seem meaningful,

whereas others seem to be too rigid, e.g. the demand for only one mechanism of action for each medication. An additional condition, not mentioned in the list above, which is that the combination should be cost effective, seems plausible but is probably difficult to fulfil, since the relevant data might not be available.

Of interest are the guidelines for using a combination based on the $n=1$ trial in clinical practice, described in the paper by Preskorn and Lacey (2007), which come very close to everyday clinical practice:

- (1) Each drug has individually been given an adequate trial and has been found to be inadequately effective
- (2) The combination meets most of the criteria for rational polypharmacy in psychiatry and, ideally, has supporting data from the literature as to its efficacy, safety and tolerability
- (3) The combination is found to be superior overall to either agent alone in terms of efficacy, safety and tolerability
- (4) After a period of stabilization, a trial is made to taper one of the agents to test the continued need for combination therapy

Irrationality probably has to be considered, if the comedication leads to reduced plasma levels of the first medication (de Leon, 2004), as is often the case during the combination of an antipsychotic with carbamazepine. However, this combination might also increase efficacy, e.g. in mania, and might then be acceptable, despite the negative pharmacokinetic interactions.

An interesting theoretical approach in this context is the concept of intra molecular polypharmacy suggested by Stahl (2008), realised in some of the 'rich drugs' like the SGAs, which are intervening in different neuropharmacological circuits, reducing not only psychotic symptoms, but also depressive symptoms (Möller, 2005). This could be seen as an indication that a more selective pharmacological intervention focussing only on the most relevant transmitter system for schizophrenia, the dopaminergic system, might not be sufficient to reduce some symptom domains of schizophrenic psychosis. If this is accepted, why not allow, instead of treatment with a rich compound, a treatment with a selective compound plus a meaningful comedication.

This line of thinking leads to other questions which can probably not be answered at present. Was the introduction of selective antidepressants, like the SSRIs, associated with an increase of comedications? Was the introduction of the antipsychotics with a rich pharmacological profile, like most SGAs, associated

Table 3. Criteria for rational co-pharmacy in psychiatry (Modified according to Preskorn and Lacey, 2007)

×	Knowledge that the combination has a positive effect on the pathophysiology of the disorder
×	Convincing evidence that the combination is more effective than monotherapy
×	The combination should not pose significantly greater safety or tolerability risks than monotherapy
×	Drugs should not interact both pharmacokinetically and pharmacodynamically
×	Drugs should have mechanisms of action that are likely to interact in a way that augments response
×	Drugs should have only one mechanism of action
×	Drugs should not have a broad-acting mechanism of action
×	Drugs should not have the same mechanism of action
×	Drugs should not have opposing mechanisms of action
×	Each drug should have simple metabolism
×	Each drug should have an intermediate half-life
×	Each drug should have linear pharmacokinetics

with a reduction in comedication? There is a strong impression that there is an increase of comedication/polypharmacy in both fields – both in the treatment of depression and in the treatment of schizophrenia.

Given the hypothesis that modern highly specific antidepressants are weaker and modern antipsychotics ('rich drugs') are stronger in their goal of efficacy than their traditional counterparts (Leucht et al., 2009; Baghai et al., 2011; Möller et al., 2012), this does not explain the general increase in comedication/polypharmacy. The increase of comedication/polypharmacy might be, at least to a certain degree, driven by reasons other than the pharmacological properties or the efficacy of the respective compounds. The increased expectations for remission and recovery might play a role, as both outcome criteria are the goal in both schizophrenia and depression. Additionally, the majority of psychiatric patients are usually treated by non-psychiatrists. Treating depression, for example, has become relatively easy these days. Primary care physicians can choose from a variety of very good first-line options, with easy dosage regimens and good tolerability profiles (usually SSRIs). Many patients will experience an improvement, if not complete remission, of their symptoms. As a consequence, the more refractory and resistant cases are left to the psychiatrists, and these are usually also the very patients requiring comedication/polypharmacy.

Another possible explanation might be that, at present, doctors stick more to the licensed dose of single compounds, possibly reducing their potential efficacy, whereas, in the past, very often much higher doses were used, which might have resulted in greater efficacy of the compounds. A reminder of this tradition is the CATIE study (Lieberman et al., 2005), where olanzapine was used up to 30 mg/p.d. (licensed dose 20 mg/p.d.); it showed the best results in this study

compared to the other antipsychotics, for which the licensed dose was respected.

Prevalence of comedication/polypharmacy

Comedication and polypharmacy seem to have been well recognized phenomena, and problems seem to have existed in earlier times, when there was no theoretically-based pharmacotherapy. This can be seen from the following quotations: 'Polypharmacy is not unique to psychiatry, or to the present era of drug treatment. Over a hundred years ago, William Osler (1898, cited in Paris, 2010) criticized his colleagues for treating patients with 'shotgun' methods, giving drugs to manage each symptom separately and focussing on symptoms rather than on a disease process. Osler's comments still apply to the practice of medicine.' (Paris, 2010). A careful literature search using the terms comedication, polypharmacy and psychopharmacology gives only a little information on the history of comedication/polypharmacy in psychiatry. Therefore, we are far away from being able to write a history of this phenomenon.

From my own experience as a doctor who has worked in psychiatry since the beginning of the 1970s, I can say that already at that time it was common practice to use certain combinations. For example, in a large state hospital close to Munich, severely acute, mostly agitated or even aggressive psychotic in-patients were treated initially with an injection combining haloperidol, chlorpromazine and promethazine. In-patients suffering from severe depression were treated with a tricyclic antidepressant and a benzodiazepine to reduce anxiety and sleep disturbances from the beginning.

The earliest systematic data in Germany are available from the years 1979–1989. They are based on the

Table 4. AMÜP drug surveillance study (1979–1989): Most frequently used neuroleptics ($n > 900$) in all patients (mean daily doses (MDD), mean duration of treatment (MDT) and combination data)

	<i>n</i>	MDD	MDT	Plus other antipsychotic	Plus biperiden	Plus antidepressant
		mg/d	d	>1 d (%)	>1 d (%)	>1 d (%)
Haloperidol	5229	15.4	26	74.8	50.9	22.3
Perazine	4778	302	32	59.4	23.2	26.3
Levomepromazine	3165	107	13	81.5	32.4	18.5
Thioridazine	1089	179	23	48.1	17.6	24.1
Fluspirilene	1019	–	–	81.2	37.9	13.5
Clozapine	967	205	46	58.6	18.2	6.3

Table 5. AMÜP drug surveillance study (1979–1989): Most frequently used antidepressants ($n > 800$) in all patients (mean daily doses (MDD), mean duration of treatment (MDT) and combination data)

	<i>n</i>	MDD	MDT	Plus BZD	Plus AP
		mg	d	>1 d (%)	>1 d (%)
Amitriptyline	2658	109	33	49	52
Clomipramine	1319	111	36	26	47
Doxepine	893	98	22	48	46
Maprotiline	863	108	32	21	38
Tranlycypromine	803	17	32	37	90**

** Mostly in the fixed combination with trifluperazine.

German drug surveillance system, Arzneimittel Überwachung Psychiatrie (AMÜP). Tables 4 and 5 show the most frequently used antipsychotics or antidepressants, respectively, as well as the doses, mean duration of treatment and some preferred drug combinations (Grohmann et al., 1994, 2004a, b).

Interestingly, in the group of haloperidol-treated patients (Table 4) the most common comedication treatment is biperiden (to reduce EPS), while clozapine is, as expected, only rarely combined with biperiden. There is a high tendency to combine one neuroleptic with another one. One reason for this is that, as pointed out above, haloperidol is often combined in acute psychotic patients with a more sedative phenothiazine like levomepromazine. Nearly all neuroleptic agents, apart from clozapine, are combined in about 20% of patients with an antidepressant, probably either for reasons of a depression or a negative syndrome.

As to the data on antidepressants (Table 5), the high prevalence of combinations with benzodiazepines – depending on the respective antidepressants between

20 and 50% – is remarkable. It seems somewhat counter-intuitive that the most sedative antidepressants such as amitriptyline and doxepine have the highest comedication. Considering that these are naturalistic data, this can probably be explained by the fact that these were patients with severe depression associated with anxiety and sleep disorders, for whom these sedative antidepressants were selected along with the benzodiazepine comedication. Results from randomized control trials (RCTs) and naturalistic studies suggest that the combination of an antidepressant compound with benzodiazepines can lead to a faster onset of action (Henkel et al., 2009), and might subsequently also be protective in terms of emergent suicidal thoughts (Seemüller et al., 2010b). The high comedication rate (around 50%) with neuroleptics is astonishing. This cannot only be due to psychotic depression, which does not have such a prevalence, but probably also to the fact, that in those days, in Germany, so called ‘low potency neuroleptics’ such as thioridazine were often prescribed as surrogates for benzodiazepines to reduce agitation and sleep disturbances.

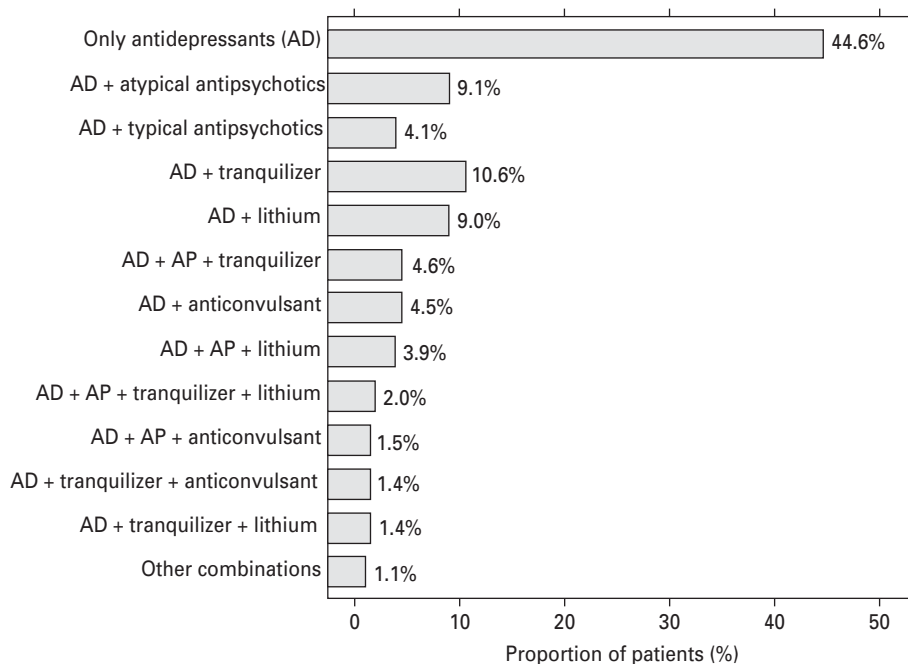


Fig. 1. Antidepressant treatment combinations at discharge from inpatient treatment ($n=1014$) (AD, antidepressant; AP, antipsychotic compound).

Table 6. AMSP Schizophrenia 2009: main combination of antipsychotics (Atyp AP=atypical antipsychotic, typ.-low potency=typical low potency antipsychotic, typ.-high potency=typical high potency antipsychotic)

	% schizo	% atyp AP
Atyp AP+typ.-low potency	32.8	39.2
Atyp AP+atyp AP	27.8	33.3
Atyp AP+typ.-high potency	20.8	24.8

Most recently, a double-blind randomized controlled trial reported significantly faster onset of the antidepressant action of citalopram when combined with doses of the low potency neuroleptic pipamperone, providing fresh evidence for this former clinical practice. The authors consider that at especially low dosages pipamperone might act as a highly potent 5-HT_{2a}/D₄ receptor antagonist, which might lead to an acceleration of the onset of action (Wade et al., 2011). In particular, the positive effect of this combination for symptoms such as sleep disturbance, reduced appetite, concentration difficulties and pessimistic thoughts seems to be responsible for this early symptom improvement (Wade et al., 2011). However, it needs to be underlined that the comedication is also often time limited. For example, in the above

mentioned naturalistic study of depressed inpatients, about 59% of all patients received a comedication with a benzodiazepine and about 45% received a comedication with an antipsychotic (Seemüller et al., 2010a). However, on discharge, comedication rates for tranquilizers (10.6%) as well as for neuroleptics (13.2%) decreased markedly (Fig. 1).

Data from the successor of the AMÜP system, the Arzneimittelsicherheit in der Psychiatrie (AMSP) (Stübner et al., 2010) cover the more recent years of pharmacopsychiatry in Germany, starting in 1994 and going up to 2009. The data, so far unpublished, show that comedication is increasing. Most remarkably, polypharmacy in the sense of more than four psychotropic medications has increased (Fig. 2). Table 6 and Figures 3–5 show details of combinations in depression and schizophrenia in a more detailed way. All this reflects the treatment strategies involved in the different university and non-university psychiatric hospitals, and means it can probably not be explained by clinical practice alone, but might have several reasons in the sense discussed above. There are not many differences in the prevalence for comedication/polypharmacy between different settings such as university hospitals, state hospitals or psychiatric departments in general hospitals. In the AMSP system psychiatric hospitals not only from Germany, but also from Austria and Switzerland are involved.

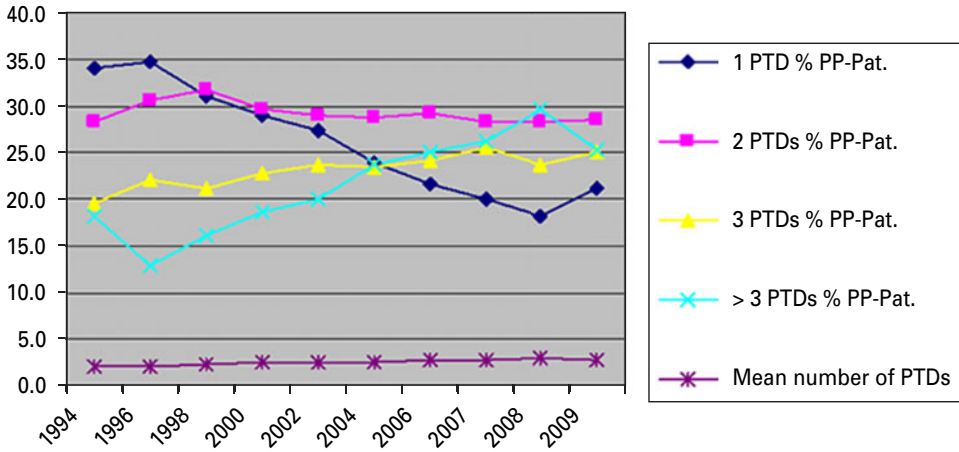


Fig. 2. Prevalence of comedication/polypharmacy with psychotropic drugs (PTD) in inpatients treated with psychopharmaca (PP). Data of the German drug surveillance system, Arzneimittelsicherheit in der Psychiatrie (AMSP).

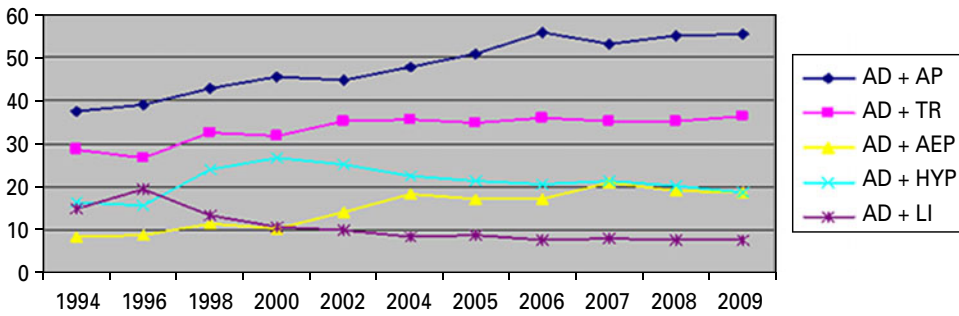


Fig. 3. Prevalence of combination of antidepressants with other psychopharmaca in % of depressed inpatients. Data of the German drug surveillance system, Arzneimittelsicherheit in der Psychiatrie (AMSP) (AD, antidepressant; AP, antipsychotic; TR, tranquilizer; AEP, antiepileptic; HYP, hypnotic; LI, Lithium).

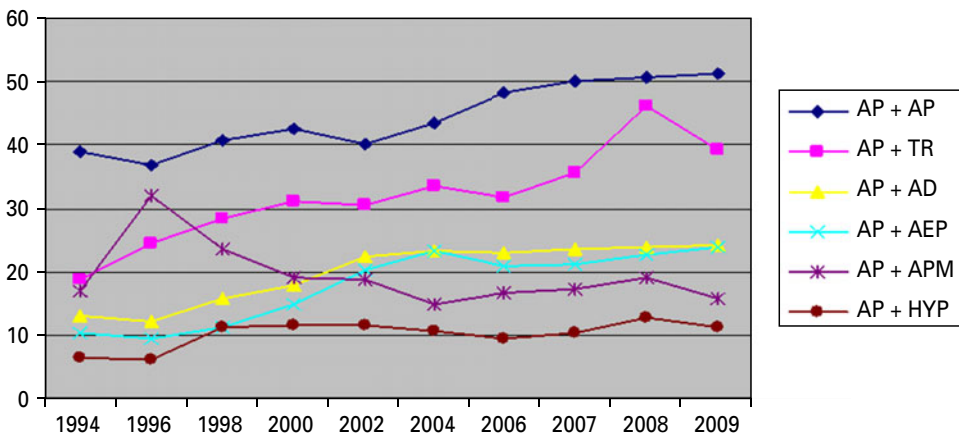


Fig. 4. Prevalence of combination of antipsychotics with other psychopharmaca in % of schizophrenic inpatients. Data of the German drug surveillance System (AP, antipsychotic; TR, tranquilizer; AD, antidepressant; AEP, antiepileptic; APM, antiparkinson medication; HYP, hypnotic).

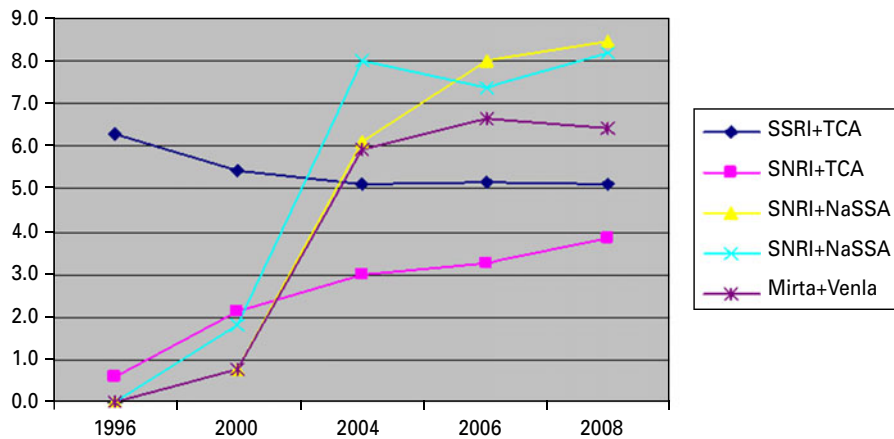


Fig. 5. Prevalence of combination of antidepressants with other antidepressants in % of depressed inpatients. Data of the German drug surveillance system, Arzneimittelsicherheit in der Psychiatrie (AMSP) (SSRI, selective serotonin reuptake inhibitor; SNRI, selective serotonin and noradrenalin reuptake inhibitor; NaSSA, noradrenergic specific serotonergic antidepressant; Mirta, mirtazapine; Venla, Venlafaxine; TCA, tricyclic antidepressant).

In Austria the number of psychotropic medications per patient tends to be somewhat higher (5.3) compared to Switzerland (4.5) und Germany (4.1). In an additional analysis it was demonstrated that, in particular, the increase above three medications is associated with a higher frequency of severe side effects and even death (Grohmann oral communication). Thus the problematic aspects of comedication/polypharmacy become obvious.

It is difficult to compare these data on the prevalence of comedication/polypharmacy with data from other studies and from other regions of the world. There are too many differences in terms of the availability of specific compounds in some countries and the way data were collected or analysed. In spite of all these methodological differences, the general outcome results might be seen as similar: a large amount of comedication/polypharmacy (Mojtabai and Olfson, 2010) often accompanied by a recent increase, similar to the above two studies from Germany. This seems to go far beyond evidence-based indications for comedication and polypharmacy (Frye et al., 2000; Kotzan et al., 2002; Stahl and Grady, 2004; Aparasu et al., 2005; Baghai et al., 2006; Gilmer et al., 2007; Haider et al., 2007; Glezer et al., 2009; Karagianis et al., 2009; McIntyre and Jerrell, 2009).

A few studies touched on the problems of pharmacokinetic interaction and increased number of side effects (Daniel et al., 1994; Heeringa et al., 1999; Freudenreich and Goff, 2002; Spina et al., 2002; Gardos, 2005; Ito et al., 2005; Tranulis et al., 2008) in connection with comedication/polypharmacy. Pharmacoeconomical issues of comedication/polypharmacy

(increase of costs) have so far not been empirically analysed very much (Clark et al., 2002; Valuck et al., 2007; Zhu et al., 2008; Poeschla et al., 2011).

Conclusions

Comedication and even polypharmacy are meaningful and rational under certain conditions (Preskorn and Lacey, 2007). From a clinical viewpoint it might probably be going too far to always ask for a proven accordance to the strict rules of evidence-based medicine, because it is too complicated to do so for all combinations judged as suitable from a clinical or theoretical perspective (Möller and Maier, 2010).

Interestingly, in a recent survey it was found that high antipsychotic polypharmacy prescribers had more clinical experience and fewer concerns about the risks of polypharmacy (Correll et al., 2011). This underlines that comedication/polypharmacy is probably not induced only by lack of knowledge. Hence, it would be naïve to ban comedication/polypharmacy *a priori*. Instead, a more differentiated understanding and approach is necessary. Comedication, and especially polypharmacy, should always be considered critically in terms of benefits and risks (Barnes and Paton, 2011), and strategies to reduce polypharmacy should be implemented (Janssen et al., 2004; Patrick et al., 2006; Thompson et al., 2008). In addition, health care costs should be taken into account. On the other hand, polypharmacy is one of the tools we have to offer to treatment-resistant and severely ill patients.

From an educational perspective the condensed thoughts suggested by Preskorn and Lacey (2007), seem meaningful:

- Mono-drug therapy: the ideal;
- Co-pharmacy: commonly needed;
- Triple pharmacy: may be necessary;
- Quadruple pharmacy: first consider that three drugs are not working.

References

- Adan-Manes J, Garcia-Parajua P (2009) Aripiprazole in combination with other antipsychotic drugs may worsen psychosis. *J Clin Pharm Ther* 34:245–246.
- Agid O, Kapur S, Remington G (2008) Emerging drugs for schizophrenia. *Expert Opin Emerg Drugs* 13:479–495.
- Alda M, Yatham LN (2009) Is monotherapy as good as polypharmacy in long-term treatment of bipolar disorder? *Can J Psychiatry* 54:719–725.
- Aparasu RR, Mort JR, Brandt H (2005) Polypharmacy trends in office visits by the elderly in the United States, 1990 and 2000. *Res Social Adm Pharm* 1:446–459.
- Arranz MJ, de Leon J (2007) Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry* 12:707–747.
- Arranz MJ, Kerwin RW (2003) Advances in the pharmacogenetic prediction of antipsychotic response. *Toxicology* 192:33–35.
- Baghai TC, Marcuse A, Brosch M, Schule C, Eser D, Nothdurfter C, Steng Y, Noack I, Pietschmann K, Moller HJ, Rupprecht R (2006) The influence of concomitant antidepressant medication on safety, tolerability and clinical effectiveness of electroconvulsive therapy. *World J Biol Psychiatry* 7:82–90.
- Baghai TC, Blier P, Baldwin D, Bauer M, Goodwin G, Fountoulakis KN, Kasper S, Leonard B, Malt U, Stein DJ, Versiani M, Möller HJ (2011) General and comparative efficacy and effectiveness of antidepressants in the acute treatment of depressive disorders: a report by the WPA Section on Pharmacopsychiatry. *Eur Arch Psychiatry Clin Neurosci* 26(Suppl. 3):207–245.
- Barbui C, Nose M, Mazzi MA, Thornicroft G, Schene A, Becker T, Bindman J, Leese M, Helm H, Koeter M, Weinmann S, Tansella M (2006) Persistence with polypharmacy and excessive dosing in patients with schizophrenia treated in four European countries. *Int Clin Psychopharmacol* 21:355–362.
- Barnes TR, Paton C (2011) Antipsychotic polypharmacy in schizophrenia: benefits and risks. *CNS Drugs* 25:383–399.
- Bauer M, Bschor T, Pfennig A, Whybrow PC, Angst J, Versiani M, Moller HJ, Disorders WT (2007) World federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. *World J Biol Psychiatry* 8:67–104.
- Biancosino B, Barbui C, Marmai L, Dona S, Grassi L (2005) Determinants of antipsychotic polypharmacy in psychiatric inpatients: a prospective study. *Int Clin Psychopharmacol* 20:305–309.
- Blier P, Ward HE, Tremblay P, Laberge L, Hebert C, Bergeron R (2010) Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. *Am J Psychiatry* 167:281–288.
- Clark RE, Bartels SJ, Mellman TA, Peacock WJ (2002) Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: implications for state mental health policy. *Schizophr Bull* 28:75–84.
- Correll CU, Shaikh L, Gallego JA, Nachbar J, Olshanskiy V, Kishimoto T, Kane JM (2011) Antipsychotic polypharmacy: a survey study of prescriber attitudes, knowledge and behavior. *Schizophr Res* 131:58–62.
- Crossley NA, Bauer M (2007) Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry* 68:935–940.
- Daniel DG, Randolph C, Jaskiw G, Handel S, Williams T, Abi-Dargham A, Shoaf S, Egan M, Elkashef A, Liboff S (1994) Coadministration of fluvoxamine increases serum concentrations of haloperidol. *J Clin Psychopharmacol* 14:340–343.
- De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ (2009) Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 24:412–424.
- de Leon J (2004) Atypical antipsychotic dosing: the effect of smoking and caffeine. *Psychiatr Serv* 55:491–493.
- Eser D, Baghai TC, Moller HJ (2007) Evidence of agomelatine's antidepressant efficacy: the key points. *Int Clin Psychopharmacol* 22(Suppl. 2):S15–S19.
- Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, Möller HJ (2005) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, Part 1: acute treatment of schizophrenia. *World J Biol Psychiatry* 6:132–191.
- Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, Möller HJ (2006) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: long-term treatment of schizophrenia. *World J Biol Psychiatry* 7:5–40.
- Fountoulakis KN, Möller HJ (2011) Efficacy of antidepressants: a re-analysis and re-interpretation of the Kirsch data. *Int J Neuropsychopharmacol* 14:405–412.
- Freudenreich O, Goff DC (2002) Antipsychotic combination therapy in schizophrenia: a review of efficacy and risks of current combinations. *Acta Psychiatr Scand* 106:323–330.

- Frye MA, Ketter TA, Leverich GS, Huggins T, Lantz C, Denicoff KD, Post RM (2000) The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. *J Clin Psychiatry* 61:9–15.
- Gardos G (2005) Antipsychotic polypharmacy or monotherapy? *Neuropsychopharmacol Hung* 7:72–77.
- Gilmer TP, Dolder CR, Folsom DP, Mastin W, Jeste DV (2007) Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999–2004. *Psychiatr Serv* 58:1007–1010.
- Glezer A, Byatt N, Cook R Jr., Rothschild AJ (2009) Polypharmacy prevalence rates in the treatment of unipolar depression in an outpatient clinic. *J Affect Disord* 117:18–23.
- Glick ID, Pham D, Davis JM (2006) Concomitant medications may not improve outcome of antipsychotic monotherapy for stabilized patients with nonacute schizophrenia. *J Clin Psychiatry* 67:1261–1265.
- Goldberg JF, Brooks JO III, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, Miklowitz DJ, Ketter TA, Sachs GS, Thase ME (2009) Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. *J Clin Psychiatry* 70:155–162.
- Gören JL, Parks JJ, Ghinassi FA, Milton CG, Oldham JM, Hernandez P, Chan J, Hermann RC (2008) When is antipsychotic polypharmacy supported by research evidence? Implications for QI. *Jt Comm J Qual Patient Saf* 34:571–582.
- Grohmann R, Rüter E, Schmidt LG (1994) Unerwünschte Wirkungen von Psychopharmaka – Ergebnisse der AMÜP-Studie. Berlin: Springer.
- Grohmann R, Engel RR, Rüter E, Hippus H (2004a) The AMSP drug safety program: methods and global results. *Pharmacopsychiatry* 37(Suppl. 1):S4–S11.
- Grohmann R, Hippus H, Helmchen H, Rüter E, Schmidt LG (2004b) The AMÜP study for drug surveillance in psychiatry – a summary of inpatient data. *Pharmacopsychiatry* 37(Suppl. 1):S16–S26.
- Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht R, Vieta E, Möller HJ (2002) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders, Part I: treatment of bipolar depression. *World J Biol Psychiatry* 3:115–124.
- Grunze H, Kasper S, Goodwin G, Bowden C, Möller HJ (2004) The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment. *World J Biol Psychiatry* 5:120–135.
- Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, Kasper S, WFSBP Task Force on Treatment Guidelines for Bipolar Disorder (2010) The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* 11:81–109.
- Haider SI, Johnell K, Thorslund M, Fastbom J (2007) Trends in polypharmacy and potential drug-drug interactions across educational groups in elderly patients in Sweden for the period 1992–2002. *Int J Clin Pharmacol Ther* 45:643–653.
- Heeringa M, Beurskens R, Schouten W, Verduijn MM (1999) Elevated plasma levels of clozapine after concomitant use of fluvoxamine. *Pharm World Sci* 21:243–244.
- Henkel V, Mergl R, Allgaier AK, Kohlen R, Moller HJ, Hegerl U (2006) Treatment of depression with atypical features: a meta-analytic approach. *Psychiatry Res* 141:89–101.
- Henkel V, Seemuller F, Obermeier M, Adli M, Bauer M, Mundt C, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, Mayr A, Moller HJ, Riedel M (2009) Does early improvement triggered by antidepressants predict response/remission? Analysis of data from a naturalistic study on a large sample of inpatients with major depression. *J Affect Disord* 115:439–449.
- Honer WG, Thornton AE, Chen EY, Chan RC, Wong JO, Bergmann A, Falkai P, Pomarol-Clotet E, McKenna PJ, Stip E, Williams R, MacEwan GW, Wasan K, Procyshyn R (2006) Clozapine alone vs. clozapine and risperidone with refractory schizophrenia. *N Engl J Med* 354:472–482.
- Ito H, Koyama A, Higuchi T (2005) Polypharmacy and excessive dosing: psychiatrists' perceptions of antipsychotic drug prescription. *Br J Psychiatry* 187:243–247.
- Janssen B, Weinmann S, Berger M, Gaebel W (2004) Validation of polypharmacy process measures in inpatient schizophrenia care. *Schizophr Bull* 30:1023–1033.
- Kapur S, Mamo D (2003) Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Prog Neuropsychopharmacol Biol Psychiatry* 27:1081–1090.
- Karagianis J, Novick D, Pecenek J, Haro JM, Dossenbach M, Treuer T, Montgomery W, Walton R, Lowry AJ (2009) Worldwide-Schizophrenia Outpatient Health Outcomes (W-SOHO): baseline characteristics of pan-regional observational data from more than 17,000 patients. *Int J Clin Pract* 63:1578–1588.
- Kasper S, Montgomery SA, Möller HJ, van Oers HJJ, Schutte AJ, Vrijland P, van der Meulen E (2010) Longitudinal analysis of the suicidal behavior risk in placebo-controlled studies of mirtazapine in major depressive disorder. *World J Biol Psychiatry* 11:36–44.
- Kennedy SH, Rizvi SJ (2010) Agomelatine in the treatment of major depressive disorder: potential for clinical effectiveness. *CNS Drugs* 24:479–499.
- Kim DH, Maneen MJ, Stahl SM (2009) Building a better antipsychotic: receptor targets for the treatment of multiple symptom dimensions of schizophrenia. *Neurotherapeutics* 6:78–85.
- Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT (2008) Initial severity and antidepressant benefits: a meta-analysis of data submitted to the food and drug administration. *PLoS Med* 5:e45. doi:10.1371/journal.pmed.0050045.
- Kotzan JA, Maclean R, Wade W, Martin BC, Lami H, Tadlock G, Gottlieb M (2002) Prevalence and patterns of concomitant use of selective serotonin reuptake inhibitors

- and other antidepressants in a high-cost polypharmacy cohort. *Clin Ther* 24:237–248.
- Laughren T, Levin R (2006) Food and drug administration perspective on negative symptoms in schizophrenia as a target for a drug treatment claim. *Schizophr Bull* 32:220–222.
- Leucht S, Kissling W, Davis JM (2009) Second-generation antipsychotics for schizophrenia: can we resolve the conflict? *Psychol Med* 39:1591–1602.
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353:1209–1223.
- McIntyre RS, Jerrell JM (2009) Polypharmacy in children and adolescents treated for major depressive disorder: a claims database study. *J Clin Psychiatry* 70:240–246.
- Megna JL, Kunwar AR, Mahlotra K, Sauro MD, Devitt PJ, Rashid A (2007) A study of polypharmacy with second generation antipsychotics in patients with severe and persistent mental illness. *J Psychiatr Pract* 13:129–137.
- Millan MJ (2009) Dual- and triple-acting agents for treating core and co-morbid symptoms of major depression: novel concepts, new drugs. *Neurotherapeutics* 6:53–77.
- Mistler LA, Mellman TA, Drake RE (2009) A pilot study testing a medication algorithm to reduce polypharmacy. *Qual Saf Health Care* 18:55–58.
- Miyamoto S, Duncan GE, Marx CE, Lieberman JA (2005) Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry* 10:79–104.
- Mojtabai R, Olfson M (2010) National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch Gen Psychiatry* 67:26–36.
- Möller HJ (2003) Management of the negative symptoms of schizophrenia: new treatment options. *CNS Drugs* 17:793–823.
- Möller HJ (2005) Antipsychotic and antidepressive effects of second generation antipsychotics two different pharmacological mechanisms? *Eur Arch Psychiatry Clin Neurosci* 255:190–201.
- Möller HJ (2008a) Is there a need for a new psychiatric classification at the current state of knowledge? *World J Biol Psychiatry* 9:82–85.
- Möller HJ (2008b) Isn't the efficacy of antidepressants clinically relevant? A critical comment on the results of the metaanalysis by Kirsch et al. 2008. *Eur Arch Psychiatry Clin Neurosci* 258:451–455.
- Möller HJ (2008c) Systematic of psychiatric disorders between categorical and dimensional approaches: Kraepelin's dichotomy and beyond. *Eur Arch Psychiatry Clin Neurosci* 258:48–73.
- Möller HJ (2009a) Antidepressants: controversies about their efficacy in depression, their effect on suicidality and their place in a complex psychiatric treatment approach. *World J Biol Psychiatry* 10:1–16.
- Möller HJ (2009b) Is evidence sufficient for evidence-based medicine? *Eur Arch Psychiatry Clin Neurosci* 259(Suppl. 2): S167–S172.
- Möller HJ (2010) Le nuove frontiere della psicofarmacologia: focus su antipsicotici e antidepressivi. In *Lezioni di Psichiatria per il nuovo Millennio* (Fiorillo A, ed), pp43–58. Roma: Il Pensiero Scientifico Editore.
- Möller HJ (2012) Pharmacotherapy of schizophrenic patients: achievements, unsolved needs, future research necessities. *Curr Pharm Biotechnol* 13:1476–1489.
- Möller HJ (2011) Current developments in psychopharmacology for the treatment of depression and schizophrenia. *Pharmacopsychiatry* 44:18–20.
- Möller HJ, Maier W (2010) Evidence-based medicine in psychopharmacotherapy: possibilities, problems and limitations. *Eur Arch Psychiatry Clin Neurosci* 260:25–39.
- Möller HJ, Riedel M, Muller N, Fischer W, Kohlen R (2004) Zolopine vs. placebo in the treatment of schizophrenic patients with stable primary negative symptoms: a randomized double-blind multicenter trial. *Pharmacopsychiatry* 37:270–278.
- Möller HJ, Bitter I, Bobes J, Fountoulakis KN, Höschl C, Kasper S (2012) Position statement of the European Psychiatric Association (EPA) on the value of antidepressants in the treatment of unipolar depression. *Eur Psychiatry* 27:114–128.
- Nelson JC, Papakostas GI (2009) Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry* 166:980–991.
- Norman TR, Burrows GD (2007) Emerging treatments for major depression. *Expert Rev Neurother* 7:203–213.
- Pandurangi AK, Dalkilic A (2008) Polypharmacy with second-generation antipsychotics: a review of evidence. *J Psychiatr Pract* 14:345–367.
- Paris J (2010) *The use and misuse of psychiatric drugs*. Oxford: Wiley-Blackwell.
- Patrick V, Schleifer SJ, Nurenberg JR, Gill KJ (2006) Best practices: an initiative to curtail the use of antipsychotic polypharmacy in a state psychiatric hospital. *Psychiatr Serv* 57:21–23.
- Poeschla BD, Bartle P, Hansen KP (2011) Serotonin syndrome associated with polypharmacy in the elderly. *Gen Hosp Psychiatry* 33:301–311.
- Preskorn SH, Lacey RL (2007) Polypharmacy: when is it rational? *J Psychiatr Pract* 13:97–105.
- Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, Nierenberg AA (2009) STAR*D: revising conventional wisdom. *CNS Drugs* 23:627–647.
- Russell PS, George C, Mammen P (2006) Predictive factors for polypharmacy among child and adolescent psychiatry inpatients. *Clin Pract Epidemiol Ment Health* 2:25.
- Schechter LE, Ring RH, Beyer CE, Hughes ZA, Khawaja X, Malberg JE, Rosenzweig-Lipson S (2005) Innovative approaches for the development of antidepressant drugs: current and future strategies. *NeuroRx* 2:590–611.

- Schmitt GJ, la Fougere C, Dresel S, Frodl T, Hahn K, Moller HJ, Meisenzahl EM (2008) Dual-isotope SPECT imaging of striatal dopamine: first episode, drug naive schizophrenic patients. *Schizophr Res* 101:133–141.
- Sedvall G, Farde L (1995) Chemical brain anatomy in schizophrenia. *Lancet* 346:743–749.
- Seemüller F, Riedel M, Obermeier M, Bauer M, Adli M, Kronmüller K, Holsboer F, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, Dichgans E, Bottlander R, Musil R, Moller HJ (2010a) Outcomes of 1014 naturalistically treated inpatients with major depressive episode. *Eur Neuropsychopharmacol* 20:346–355.
- Seemüller F, Schennach-Wolff R, Obermeier M, Henkel V, Moller HJ, Riedel M (2010b) Does early improvement in major depression protect against treatment emergent suicidal ideation? *J Affect Disord* 124:183–186.
- Shelton RC, Osuntokun O, Heinloth AN, Corya SA (2010) Therapeutic options for treatment-resistant depression. *CNS Drugs* 24:131–161.
- Sommer IE, Begemann MJ, Temmerman A, Leucht S (2012) Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: a quantitative literature review. *Schizophr Bull* 38:1003–1011.
- Spina E, Avenoso A, Scordo MG, Ancione M, Madia A, Gatti G, Perucca E (2002) Inhibition of risperidone metabolism by fluoxetine in patients with schizophrenia: a clinically relevant pharmacokinetic drug interaction. *J Clin Psychopharmacol* 22:419–423.
- Stahl SM (1999a) Antipsychotic polypharmacy, Part 1: therapeutic option or dirty little secret? *J Clin Psychiatry* 60:425–426.
- Stahl SM (1999b) Antipsychotic polypharmacy, part 2: tips on use and misuse. *J Clin Psychiatry* 60:506–507.
- Stahl SM (2008) Personalized medicine, pharmacogenomics, and the practice of psychiatry: on the threshold of predictive therapeutics in psychopharmacology? *CNS Spectr* 13:115–118.
- Stahl SM, Grady MM (2004) A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. *Curr Med Chem* 11:313–327.
- Stübner S, Grohmann R, von Stralendorff L, Ruther E, Moller HJ, Muller-Oerlinghausen B, Engel RR, Horvath A, Greil W (2010) Suicidality as rare adverse event of antidepressant medication: report from the AMSP multicenter drug safety surveillance project. *J Clin Psychiatry* 71:1293–1307.
- Suzuki T, Uchida H, Watanabe K, Nakajima S, Nomura K, Takeuchi H, Tanabe A, Yagi G, Kashima H (2008) Effectiveness of antipsychotic polypharmacy for patients with treatment refractory schizophrenia: an open-label trial of olanzapine plus risperidone for those who failed to respond to a sequential treatment with olanzapine, quetiapine and risperidone. *Hum Psychopharmacol* 23:455–463.
- Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ Jr., Okasha A, Singh B, Stein DJ, Olie JP, Fleischhacker WW, Moeller HJ (2008) World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res* 100:20–38.
- Thompson A, Sullivan SA, Barley M, Strange SO, Moore L, Rogers P, Sipos A, Harrison G (2008) The DEBIT trial: an intervention to reduce antipsychotic polypharmacy prescribing in adult psychiatry wards – a cluster randomized controlled trial. *Psychol Med* 38:705–715.
- Tranulis C, Skalli L, Lalonde P, Nicole L, Stip E (2008) Benefits and risks of antipsychotic polypharmacy: an evidence-based review of the literature. *Drug Saf* 31:7–20.
- Valuck RJ, Morrato EH, Dodd S, Oderda G, Haxby DG, Allen R (2007) How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. *Curr Med Res Opin* 23:2567–2576.
- Viola R, Csukonyi K, Doro P, Janka Z, Soos G (2004) Reasons for polypharmacy among psychiatric patients. *Pharm World Sci* 26:143–147.
- Wade AG, Crawford GM, Nemeroff CB, Schatzberg AF, Schlaepfer T, McConnachie A, Haazen L, Buntinx E (2011) Citalopram plus low-dose pipamperone vs. citalopram plus placebo in patients with major depressive disorder: an 8-week, double-blind, randomized study on magnitude and timing of clinical response. *Psychol Med* 41:2089–2097.
- Whitehead C, Moss S, Cardno A, Lewis G (2002) Antidepressants for people with both schizophrenia and depression. *Cochrane Database Syst Rev* 162(1):19–24.
- Zhu B, Ascher-Svanum H, Faries DE, Correll CU, Kane JM (2008) Cost of antipsychotic polypharmacy in the treatment of schizophrenia. *BMC Psychiatry* 8:19.