Driving performance under treatment of most frequently prescribed drugs for mental disorders: a systematic review of patient studies

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Abstract

Background: Mobility is important for daily life functioning with particular challenges regarding road safety under pharmacological treatment in patients with a psychiatric disease.

Methods: According to PRISMA guidelines, a systematic literature search on PubMed database (January 1970 till December 2020) was performed. Primary endpoints were driving performance in on-road-tests, driving simulator performance or psychomotor and visual perception functions assessed to estimate fitness to drive according to legal regulations in patient studies.

Results: Forty studies were identified (1533 patients, 38% female, median age 45 years), more than 60% were cross-sectional and open label trials. Under steady state medication 31% (range 27%-42.5%) of schizophrenic or schizoaffective patients under antipsychotics, and 18% (range 16%-20%) of unipolar and bipolar patients under antidepressants showed severe impairment in skills relevant for driving. Data point to an advantage of second generation antipsychotics (SGAs) compared to first generation antipsychotics (FGAs) as well as modern antidepressants over tricyclic antidepressants (TCAs) with respect to driving. Most patients significantly improved or stabilized in driving skills within 2-4 weeks of treatment with non-sedative or sedative antidepressants. Diazepam significantly worsened driving the first three weeks after treatment initiation, whereas medazepam (low-dose), temazepam and zolpidem did not impair driving. In long-term users of sedating antidepressants or benzodiazepines impairments in on-road–tests were not evident.
**Conclusion:** Available evidence suggests that psychopharmacologic medicines improve or at least stabilize driving performance of patients under long-term treatment when given on clinical considerations. To enhance treatment compliance, existing classification systems of medicinal drugs concerning their impact on driving performance should also incorporate information about effects of long-term treatment.

Key words: Driving performance, Benzodiazepines, Antipsychotics, Antidepressants, Mood-Stabilizers
Introduction

Modern societies demand a high grade of mobility and there is evidence that driving cessation, e.g. in cases of ageing or chronic illness, affects social and economic well-being with impact on health functioning (Edwards et al., 2010). About 67% of patients with a psychiatric disease have a drivers’ license, 77% of these patients report to drive regularly with their cars and most of them (88%) use prescribed medication. Closer inspection of data also indicates that driving restrictions largely affect social functioning of these patients (Brunnauer et al., 2016). Thus, road safety under pharmacological treatment is of great relevance for patients with a psychiatric disease and is therefore frequently asked in clinical practice.

Besides their major mode of action medicinal drugs can impair behavior most frequently because of sedating CNS adverse effects like e.g. drowsiness or inability to concentrate. Behavioral correlates of drug induced impairments may be a disruption of neuropsychological processes controlling behavior. Evidence supporting the concept of behavioral toxicity (e.g. DiMascio and Shader 1968, Hindmarch 1994) comes from epidemiological data. Albeit causal relationships can hardly be drawn, there is considerable evidence that the use of psychoactive drugs is associated with an increased risk of traffic injuries, with a particular high concern regarding benzodiazepines and tricyclic antidepressants (e.g. Ray et al., 1992; Barbone et al., 1998; Leveille et al., 1994; Mura et al., 2003; Bramness et al., 2008; Dassanayake et al., 2011; Elvik, 2013). Especially elderly users of sedating antidepressants have a more than two-fold increased risk of being involved in road traffic accidents (Ray et al., 1992; Leveille et al., 1994; Dassanayake et al., 2011). Benzodiazepine use and the association with traffic accidents seems to be more
frequent in younger drivers and risk markedly increased by co-ingestion of alcohol (Dassanayake et al., 2011).

Empirical evidence from experimental studies also indicates that behavioural toxicity, with particularly sedating CNS effects in the acute phase of treatment, is of major concern with respect to driving performance (Ramaekers, 2003; Rapoport and Banina, 2007; Berghaus et al., 2010; Strand et al., 2016; Brunnauer and Laux, 2017). However, cognitive dysfunction per se is also a core feature of many psychiatric disorders that is prominent in untreated patients and thus not necessarily linked to medication effects (Rock et al., 2014; Millan et al., 2012). Besides, there is evidence that long-term treatment with e.g. antidepressants or antipsychotics may help to improve psychomotor and cognitive dysfunction in patients with a psychiatric disease (Keefe et al., 2007, 2014; Woodward et al., 2005; Baune and Renger, 2014; Rosenblat et al., 2015; Nielsen et al., 2015; Prado et al. 2018).

Taken together stabilizing effects of pharmacological treatment have to be weighed against possible detrimental cognitive, vegetative-somatic and psychomotor effects when validating drugs with respect to driving performance. Usually studies on this topic have investigated acute effects of medicines in healthy subjects that may be quite different from issues of long-term treatment of patients. Thus, the crucial question of which pharmacological treatment patients benefit most with respect to driving performance can only be validly answered by patient studies.

This systematic review gives an update of available evidence of patient studies on treatment effects of most frequently prescribed psychotropic drugs on driving ability in psychiatric patients.
Methods

A systematic literature search in the PubMed database (January 1970 to December 2020) was performed using a combination of subject headings and keyword terms, that were: “driving performance”, “driving ability”, “driving skills”, “fitness to drive”, “traffic safety”, “on the road driving test”, “driving simulation” AND “antidepressants”, “antipsychotics” “benzodiazepines”, “Z-drugs”, “MAO-inhibitors”, “mood-stabilizers”. Furthermore, combinations of additional search terms were included to screen for further articles (search terms are listed in Supplementary Material). The titles and, if relevant, the abstracts of each citation were screened manually, and the full texts of relevant citations were then analysed in detail. Besides, reference lists were manually searched for relevant studies. All identified articles were screened and, if necessary, discussed by two independent reviewers (Drs Brunnauer and Herpich).

Types of outcome measures

We integrated evidence of various research methodologies that focused on driving performance in psychiatric patients. Articles were selected if they (i) examined driving performance in an on-road test in real traffic or in a simulated on-road test, i.e. on a closed circuit, or (ii) with a driving simulator with at least medium complexity, i.e. a fixed hardware consisting of a steering wheel, brake pedals and simulated road environment; (iii) besides studies were included, that investigated psychomotor and visual perception functions to investigate driving skills according to legal regulations.

Articles in English or German language, in which study design, sample and methods used had been described adequately, were considered for this review. Search results and study selection process are summarized in the following PRISMA flowchart (see figure 1).
Results

Study selection

A total of 1,417 hits were identified using the search terms mentioned above. The screening of titles, abstracts and in a final step the analysis of the full text articles of this literature search revealed 39 articles assessing driving ability with methodologies described above. Reference lists of included studies and related reviews did not lead to an inclusion of further studies. Personal communication led to an inclusion of one further study.

Study description

Forty studies were identified according to selection criteria. Patients were diagnosed according to ICD-10, DSM-III-R or DSM-IV criteria. Additionally, a smaller part of patients met criteria by structured interviews and rating scales. Studies consisted of 25 cross-sectional or open label trials, three randomized controlled studies and 12 investigations in a (randomized) double-blind design. The distribution of patients investigated in an inpatient setting (40%) was comparable to those investigated in an outpatient setting (42%); in 18% of studies under review the treatment setting was not specified.

Antipsychotics. Twelve studies were included in this review with schizophrenic, schizoaffective, manic depression and borderline patients. The median sample size was 31 (range 22-120) with a total of 536 patients (37% females). The median age was 33 years (range 18-62). All investigations were designed as comparative clinical trials (cross sectional and open label).
Antidepressants. The effects of antidepressants on driving performance were assessed in 14 clinical studies comprising 587 patients with primarily depressive disorders (44% female) with a median age of 45 years (range 18-78). Eight of these trials investigated driving performance within an open label design, in 6 trials patients were randomly assigned to treatment groups (four under double-blind conditions).

Mood-Stabilizers. Three publications were identified investigating driving performance in bipolar and unipolar patients and a group of patients with Meniere’s disease. A total of 60 patients was investigated (48% female) with a median age of 45 years (range18-63). Studies were designed as cross-sectional or open-label trials.

Benzodiazepines and Z-drugs. Eleven studies investigated the effects of benzodiazepines or Z-drugs on driving performance in patients with an anxiety disorder or patients with insomnia. The median sample size was 18 (range 12-44) with a total of 407 patients (22% females). Median age was 40 years (range 18-50) in the groups treated with tranquilizers and 55 years (range 25-75) in studies investigating hypnotics. Most studies were designed as (randomized) double-blind cross-over trials. An overview of studies included is provided in table 1.

Antipsychotics

Comparative clinical studies

Psychomotor functions according to legal regulations or driving simulator performance, under long-term-treatment with antipsychotic monotherapy were solely investigated within a naturalistic non-randomized design and patients were not investigated before and after treatment with respect to driving performance.
Under long-term treatment with antipsychotics and stabilized psychopathological conditions, schizophrenic and schizoaffective patients showed in 31% (27%-42.5%) of cases severe impairments in psychomotor functions related to driving skills. Second generation antipsychotics (SGAs) seemed to be advantageous compared to first generation antipsychotics (FGAs). Twenty-three percent (15%-27%) of patients treated with SGAs compared to 42% (34%-60%) of patients treated with FGAs showed severe impairments (Brunnauer et al., 2004, 2005, 2009, 2012; Soyka et al., 2005). Differences could also be seen on driving simulator performance with better results in patients under SGAs compared to FGAs in a risk simulation (Brunnauer et al., 2005, 2009). Albeit in one study an advantage of clozapine on reactivity within SGAs could be shown (Brunnauer et al., 2004), altogether, no relevant differences with respect to driving performance between SGAs investigated was evident (Brunnauer et al., 2009; Brunnauer and Laux, 2012).

Treatment combinations

While polydrug treatment is frequent in clinical practice, only a few studies could be identified that investigated driving performance under common psychopharmacologic treatment combinations in schizophrenic or schizoaffective patients. Irrespective of drug regimen, most patients do not seem to reach the level of psychomotor or driving simulator performance of healthy controls following subchronic or long-term polydrug treatment and psychopathologic stabilization (Hobi et al., 1981; Grybel-Mathyl, 1987; Wylie et al., 1993; Soyka et al., 2005; Fuermaier et al., 2019). In clinical routine settings, where patients additionally to treatment with SGAs or FGAs were co-medicated with lithium, valproate, hypnotics or antidepressants, 32%-54% of patients showed a very low test performance in functional domains relevant for driving, with a better performance of patients under polydrug treatment with SGAs (Grabe et al., 1999; Kagerer et al., 2003).
Antidepressants

Trizyclic antidepressants (TCAs)/Amitriptyline. The acute and subchronic effects of low dose nocturnally administered amitriptyline on driving performance have been investigated in chronic pain patients. Amitriptyline acutely impaired performance in an on-the-road driving test that diminished after subchronic treatment. It is important to note that patients’ pain intensity ratings were unexpectedly low and moreover did not diminish under amitriptyline treatment; thus, there might have been a selection bias with respect to participating subjects (Veldhuizen et al., 2006).

Agomelatine. A novel approach to treat depression, focusing on circadian rhythms by melatonergic mechanisms has been the development of agomelatine. After 4 weeks of treatment, patients significantly improved both in symptomatology and psychomotor skills relevant for driving, with most benefits occurring within the first two weeks of treatment. A functional level in psychomotor performance comparable to healthy controls could not be reached at the end of the four-week study phase. In the on-the-road driving test in real traffic, patients were not significantly inferior to healthy controls and could in most cases be rated as sufficiently fit to drive by a licensed driving instructor after four weeks of treatment (Brunnauer et al., 2015).

Mirtazapine. Psychomotor- and driving simulator performance in depressive patients during 14 days of treatment significantly improved under the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, indicating, that partly remitted depressed patients show a better driving performance compared to untreated patients. Performance level in psychomotor functions of healthy controls was not reached within the subchronic or long-term treatment phase (Brunnauer et al., 2008). However, after two weeks of treatment differences compared to healthy controls were not evident in driving simulator performance (Brunnauer et al., 2008; Shen et al., 2009).
Reboxetine. The effects of the selective noradrenergic reuptake inhibitor (NARI) reboxetine on psychomotor function and driving simulator performance were investigated in a randomized comparative clinical study in patients with major depression. After 14 days of treatment, patients improved in driving skills, especially in tests measuring selective attention and reactivity. Furthermore, the frequency of accidents in the risk simulations with a driving simulator markedly decreased. Although patients were still inferior to healthy control subjects in psychomotor performance after 14 days of treatment, no differences could be shown in the driving-simulator tasks (Brunnauer et al., 2008).

Trazodone. Patients with primary insomnia treated with nocturnally administered trazodone performed slightly worse in a short-term memory task, verbal learning, body sway, and arm muscle endurance. Negative effects on driving simulator performance were not found within seven days of treatment. There was, however, a high dropout-rate; 47 out of 63 individuals did not complete the entire study (Roth et al., 2011).

Venlafaxine. Four weeks of treatment with the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine had positive effects on depressive symptoms and driving skills, most improvements observable in the first two weeks. Albeit patients did not achieve healthy controls performance in psychomotor tasks within four weeks of treatment, significant differences could not be seen in an on-road-test in real traffic, when compared with healthy subjects’ performance (Brunnauer et al., 2015).

Comparative clinical studies

The effects of long-term treatment with antidepressant monotherapy on psychomotor function in a clinical routine setting were investigated by Brunnauer et al. (2006). Sixteen percent of inpatients under pharmacologic steady state conditions and prior to discharge showed severe impairments and had thus to be estimated as “unfit-to-drive”. Controlling for
confounding factors, in total 28% of patients passed psychomotor performance tests without major impairments, 10% treated with TCAs and 37.5% with modern antidepressants.

Performance in on-road-tests was assessed in two studies indicating that patients treated with selective serotonin reuptake inhibitors (SSRIs) or the SNRI venlafaxine were inferior to healthy controls. Differences between treatment groups could not be shown and driving impairment was significantly less in the treatment group, when compared to untreated depressive patients (Wingen et al., 2006; van der Sluiszen et al., 2017b).

Treatment combinations

Grabe et al. (1998) did not identify differences between patients treated with TCAs, SSRIs, monoamine oxidase inhibitors (MAOIs) and common co-medications, whereas Brunnauer and Laux (2003) have shown less psychomotor performance impairment in patients treated with SSRIs and co-medication – about 37% were without major impairment - compared to treatment with TCAs (12%). No differences, when compared to healthy control subjects could be shown in driving simulator performance (Hobi et al., 1981, Miyata et al., 2018), as well as in an on-road test with patients treated long-term (>3 years) with sedating antidepressants, combined with TCAs, SGAs or modern antidepressants (van der Sluiszen et al., 2020).

The combined use of fluoxetine or moclobemide and benzodiazepines has been differentially assessed in an on-road test by Ramaekers et al. (1997). In this study, 79% under fluoxetine and 73% under moclobemide additionally used benzodiazepines during treatment. Post-hoc analysis revealed that besides a linear decrease in driving performance throughout the treatment period in both groups, there was an apparent difference in patients taking competitive benzodiazepine co-medication metabolized by a P450 isozyme subject to inhibition by the antidepressant. Patients treated with fluoxetine decreased in driving performance until week three of treatment that diminished at week six; under fluoxetine and...
competitive benzodiazepine treatment a decline throughout the 6-week treatment period could be seen.

**Mood Stabilizers**

Comparative clinical studies

Seventeen percent of euthymic bipolar patients under long-term treatment with lamotrigine or lithium were severely impaired in psychomotor function relevant for driving, with a considerable advantage for patients treated with lamotrigine (Segmiller et al., 2013). Significant impairments, when compared to healthy controls, could also be shown in driving-simulator performance of bipolar and unipolar patients on stable lithium therapy (Hatcher et al., 1990; Jauhar et al., 1993).

**Benzodiazepines and Z-drugs**

Tranquilizers

*Diazepam*. Outpatients suffering from anxiety disorders showed a significant impairment in the first three weeks of treatment in an on-road driving test that diminished after week three (van Laar et al., 1992).

*Medazepam*. Subchronic treatment with medazepam in anxious patients showed that driving simulator performance was not adversely affected, while in a simulated on-road test, a minor increase of errors was discerned. As the author states, mean dosages were in a very low therapeutic level and thus general conclusions with respect to treatment effects should be drawn cautiously (Moore, 1977).
Hypnotics

Flunitrazepam. Patients with insomnia experienced a slight impairment of driving performance in an on-road test when treated for seven days with flunitrazepam (Schmidt et al., 1986). On the contrary, a single dose administered upon retiring to bed to patients with insomnia did not significantly affect driving performance the next morning (Vermeeren et al., 1995).

Flurazepam. Flurazepam had acute effects on driving performance in patients with insomnia. The ability to control the lateral position of the vehicle was significantly impaired and the degree of impairment was more pronounced in female subjects. Moreover, impairment was greater in the morning (10 to 11 hours) than in the afternoon (16 to 17 hours) after administration (Brookhuis et al., 1990).

Lormetazepam. Acute treatment with lormetazepam 1mg did not impair driving performance in an on-road test of patients with insomnia when tested 10 to 11 hours and 15 to 16 hours post administration. However, seven days bedtime administration of lormetazepam 1mg in primary insomnia patients induced significant impairment in driving simulator performance (Staner et al., 2005). Acute treatment with 2mg impaired driving performance of insomniacs 10 to 11 hours post ingestion, but no residual effects after 15 to 16 hours were evident (Brookhuis et al., 1990).

Temazepam. There were no significant residual effects on performance in a driving simulation test 5.5 hours after intake of temazepam the next morning (Partinen et al., 2003) and no decrease of driving performance on an on-road test was found in patients with sleep disorder that received temazepam once a night for 7 days (Schmidt et al., 1986).
Zolpidem. Single dose administration as well as repeated (7 days) treatment with zolpidem given at nighttime did not impair on-road- or driving-simulator performance of insomnia patients (Vermeeren et al. 1995; Partinen et al., 2003; Staner et al., 2005).

Zopiclone. A single oral overnight dose of zopiclone significantly impaired on-road driving performance in insomnia patients who chronically used hypnotics as well as in patients who not or only infrequently used hypnotics. However, the magnitude of impairment was less in the chronic users’ group (Leufkens et al., 2014a). Analogous results were obtained by Staner et al. (2005) who showed that single bedtime administration of zopiclone induced next day driving impairments on a driving simulator.

Comparative clinical studies

Actual driving performance and driving-related skills of elderly chronic hypnotic users were investigated by Leufkens et al. (2014b). Patients were divided in frequent users (using hypnotics ≥ 4 nights per week) and infrequent users (using hypnotics ≤ 3 nights per week). Driving, measured by a standardized highway driving and a car-following test, was not impaired in patients with insomnia, irrespective of the frequency of use of hypnotics.

Treatment combinations

Van der Sluiszen et al. (2019) suggested that in elderly patients impairment of driving performance was dependent on treatment duration. While the ability to drive was significantly impaired in patients treated with hypnotics and comedication for less than three years, no deterioration was found in patients treated for more than three years. In long-term users (> 6 month) of anxiolytics and comedication no clinically relevant differences in driving performance, compared to healthy controls, were evident.
Table 2 gives an overview of controlled experimental patient studies on antipsychotics, antidepressants, mood stabilizers, benzodiazepines, Z-drugs and driving performance.

Discussion

Summary of findings

Only 40 studies could be found according to our selection criteria, indicating a clear lack of patient studies on driving performance under psychopharmacologic treatment. No data were available that give information about causal relationships between antipsychotics, MAOIs, mood stabilizers and driving performance.

Antipsychotics

Overall, with regard to antipsychotic medication a great proportion of schizophrenic and schizoaffective patients does not reach the level of psychomotor or driving simulator performance of healthy controls following long-term treatment, despite significant clinical improvement (Wylie et al., 1993; Soyka et al., 2005; Fuermaier et al., 2019). Keeping in mind the great heterogeneity between studies, on average 31% (27%-42,5%) of in-patients showed severe impairment of psychomotor function relevant for driving under steady state pharmacological conditions prior to hospital discharge, i.e. patients were treated in most cases six weeks and more in a stationary setting (Brunnauer et al., 2004, 2005, 2009, 2012; Soyka et al., 2005). Considering, that about 32% of young, unmedicated schizophrenic patients showed severe impairment of psychomotor skills relevant for driving (Segmiller et
al., 2017) it can be assumed that impairments under steady state pharmacologic conditions may be primarily due to the illness itself than to treatment effects.

Under common treatment combinations a greater proportion of patients (32%-54%) showed severe impairment in functional domains relevant for driving (Grabe et al., 1999; Kagerer et al., 2003). As a polypharmacological approach is often administered in difficult-to-treat patients with poor treatment response, a selection bias towards a more severe clinical course might be discussed.

It is still a matter of debate, whether SGAs have an advantage with respect to psychomotor function and cognition, when compared with FGAs (e.g. Keefe et al., 2007). In this review, better driving performance was related to treatment with SGAs – amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, zotepine – compared to FGAs – haloperidol, flupenthixol, zuclopenthixol (Brunnauer et al., 2004, 2005, 2009, 2012; Soyka et al., 2005). Under polydrug treatment an advantage for SGAs was also evident (Grabe et al., 1999; Kagerer et al., 2003). Albeit there was a slight advantage of patients treated with clozapine in psychomotor skills relevant for driving in one study (Brunnauer et al., 2004), altogether, differences between SGAs with respect to driving performance could not be shown (Brunnauer et al., 2009; Brunnauer and Laux, 2012).

**To sum up:** On average, one third of schizophrenic or schizoaffective patients under treatment with antipsychotics showed severe impairment in skills relevant for driving, when compared with healthy controls, which may be primarily due to residual symptoms of the illness itself than to negative side effects of antipsychotic treatment. Studies point to an advantage of SGAs compared to FGAs with respect to driving skills and there seems to be a disadvantage under antipsychotic polypharmacy. However, conclusions must be drawn cautiously with regard to the marked methodologic heterogeneity of the studies. Moreover, interpretation of data is also limited since adverse effects of pharmacological treatment and illness-associated impairment can not be disentangled within studies under review.
Antidepressants and mood-stabilizers

About 16% of patients with major depression and 17% of bipolar patients showed severe impairment in psychomotor skills relevant for driving under long-term monotherapy with antidepressants or mood-stabilizers (Brunnauer et al., 2006; Segmiller et al., 2013). Data point to an advantage of treatment with modern antidepressants and SSRIs in particular over TCAs with regard to driving skills (Brunnauer and Laux, 2003; Brunnauer et al., 2006). Albeit Ramaekers et al. (1997) could show, that specific combinations of antidepressants with benzodiazepines may have deleterious effects on driving performance, there is also evidence, that under treatment combinations with lithium, carbamazepine, neuroleptics and hypnotics, when given on clinical considerations, a similar distribution of patients showing severe impairment (18%-20%) compared to patients under antidepressive monotherapy could be observed (Grabe et al., 1998; Brunnauer and Laux, 2003).

Acute treatment with amitriptyline, but not subchronic treatment had negative effects on on-road performance of insomnia patients (Veldhuijzen et al., 2006). Under trazodone no impairment in driving simulator performance could be seen in the acute treatment phase (Roth et al., 2011).

Patients significantly improved in psychomotor functions and driving simulator performance under subchronic or long-term treatment with agomelatine, mirtazapine, reboxetine or venlafaxine (Brunnauer et al., 2015, 2008; Shen et al., 2009). Results with respect to achievement of functional level of healthy controls in driving simulator- or on-road-performance are mixed, showing either lower performance (Wingen et al., 2006; van der Sluiszen et al., 2017b) or no significant differences (Hobi et al., 1981; Brunnauer et al., 2008, 2015; Miyata et al., 2018; van der Sluiszen et al., 2020).

No patient data were available that give information about causal relationships of SSRI monotherapy on driving ability in patients.
Under long-term treatment with lithium unipolar- and bipolar patients showed a significant lower performance than matched healthy volunteers in driving-simulator performance and there seems to be an advantage when treated with lamotrigine compared to lithium (Hatcher et al. 1990; Jauhar et al., 1993; Segmiller et al., 2013).

**To sum up:** Patients definitively profit within 2-4 weeks from treatment with antidepressants with respect to driving performance and data point to an advantage when treated with modern antidepressants over TCAs, and lamotrigine over lithium. Albeit level of psychomotor performance of healthy controls was in at least a subgroup of (partly)remitted patients not reached, differences in driving simulator performance or on-road tests are less pronounced or even do not exist and thus may be an indication for compensational competencies with respect to driving performance under “real world context”. Not least, there is also evidence that effects of sedating antidepressants on driving performance attenuate over time. Co-administration of other psychotropic medicines to antidepressants, when given on clinical considerations, seems not to be inferior when compared with trials on monotherapy.

Benzodiazepines and Z-drugs

**Tranquilizers**

Elderly patients that were treated long-term (>6 month) under clinical conditions, i.e. most were comedicated with antidepressants or antipsychotics, did not differ in driving performance, when compared with age matched healthy controls (van der Sluiszen et al., 2019). Results of controlled experimental studies suggest that subchronic or long-term treatment with low-dose medazepam did not impair on-road-driving performance of anxious patients (Moore 1977). However, deleterious effects on driving performance in an on-road-test could be shown the first 3 weeks of treatment with diazepam (van Laar et al., 1992).
Hypnotics

Most studies investigated effects of hypnotics either in a single-dose regimen or after 7 days of treatment in patients with insomnia. Temazepam and zolpidem seem to be free of acute negative effects on driving performance when given to patients with a sleep disorder (Vermeeren et al., 1995; Partinen et al., 2003; Staner et al., 2005). Zopiclone, flurazepam and dose dependent lormetazepam cause significant driving impairment in the acute treatment phase of patients with insomnia (Brookhuis et al., 1990; Staner et al., 2005; Leufkens et al., 2014a). Flunitrazepam when given as a single nocturnal dose seems to be free of deleterious effects on driving performance the next morning (Vermeeren et al., 1995); this seems however not to be true when treated for seven consecutive days (Schmidt et al., 1986).

There is some evidence, that frequency of hypnotic intake seems not to play a major role with respect to driving performance in elderly patients (Leufkens et al., 2014b), and that in chronic elderly users (>3 years) no driving impairments seem to become evident (van der Sluiszen et al., 2019). This is in line with studies indicating development of tolerance over time in long-term users (Pomara et al., 2015; van der Sluiszen et al., 2017a). However, there is also evidence that tolerance with respect to skills relevant for driving may be only partial (van der Sluiszen et al., 2017a).

To sum up: Diazepam significantly worsened driving the first three weeks of treatment, whereas low-dose medazepam did not impair driving. Among hypnotics, flunitrazepam, flurazepam, lormetazepam (dose dependent) and zopiclone significantly impaired driving performance at treatment initiation, whereas temazepam and zolpidem were found to be free of deleterious effects in patients with insomnia. There is evidence in long-term-users that impairing effects on driving attenuate over time, which however may be only partial.
Limitations

Major limitations of the current analysis are the small data base and methodological constraints - 60% of studies were cross sectional or open label trials, that do not allow to disentangle treatment effects from illness associated impairment. Included studies show large variations with study designs, patient characteristics and methodology used to measure driving performance. Besides, poor description of patient samples, with respect to clinical data, e.g. psychopathologic symptoms at time of testing, duration of illness or driving characteristics are missing in most cases. Thus, because of heterogeneity of studies the summarized evidence was not suitable for a meta-analytic approach. It should also be noted that the literature review was restricted to PubMed database. Albeit screening of reference lists of included studies and related reviews did not lead to an inclusion of further studies in our review it could be argued, that the utilization of other databases might have provided additional information. Considering all these shortcomings, conclusions of this review should be drawn cautiously.

Conclusion

Much more controlled patient studies are needed to analyse the complex relationship between illness and medication in order to clarify a core issue that is, from which pharmacologic treatment benefit patients, also with respect to driving performance. The current synopsis gives evidence, that psychopharmacologic medicines under review improve or at least stabilize driving performance of patients, when treated long-term under clinical considerations. To enhance treatment compliance and give information to professionals, patient-information-leaflets as well as classification-systems of potential driving impairing medicines should also incorporate information about stabilizing effects of long-term-treatment on driving performance and recommendations on passage of time that should be considered to minimise possible detrimental effects.
Due to the fact that particular drugs can place patients at risk - at least after treatment initiation - during everyday activities like driving a car, it is of crucial importance to ensure that physicians are aware of this and try to minimize potential disruptive effects on neuropsychological processes. Prescribers of drugs should be recommended to minimise the number of prescribed drugs, keeping in mind potential pharmacokinetic interactions, adjust dosage regimens according to a patient’s individual response and to administer medicines in nocturnal doses whenever possible – e.g. in the case of sedating antidepressants - to mitigate adverse side effects on driving performance. Not least patients should be educated on the potential risks of psychopharmacological treatments with respect to driving to attain a better awareness and self-monitoring on possible adverse drug effects.

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Drs Brunnauer and Herpich conducted the search, data extraction, and data analysis. All authors contributed to the interpretation of results and manuscript writing.

Statement of interest

Concerning the last three years AB, FH and GL have no conflicts of interest to declare for this study. PZ has received speaker fees or honoraria for advisory board participation over the last three years from Janssen Pharmaceuticals, Schwabe, Servier, and Neuraxpharm. All these affiliations have no relevance to the work covered in the manuscript.
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Table 1: Summary of patient studies included using (simulated) on-road-driving tests [(S)ORT], driving simulators [DS] or investigating psychomotor performance according to legal regulations [PP]

| Authors (year)   | Investigational drugs                          | Dose                 | Status                       | Age (y) | Design | Test | Outcome*                                                                 |
|------------------|-----------------------------------------------|----------------------|------------------------------|---------|--------|-----|--------------------------------------------------------------------------|
| **Comparative clinical studies**                                                                                     |                     |                               |         |        |     |                                                                         |
| Wylie et al. (1993) | Flupenthixol (dec.) Fluphenazine (dec.) + procyclidine comedication | n. spec.             | Schizophrenic patients (n=22) | 21-62   | Other  | DS  | ➢ Long-term treatment (n. spec.) = significant lower performance of patients when compared with healthy controls<br➤ No difference between treatment groups |
| Soyka et al. (2001) | Haloperidol Risperidone (8 patients received biperiden comedication) | 5-30mg 2-6mg         | Schizophrenic patients (n=26) | 21-46   | Other  | PP  | ➢ Long-term treatment (n. spec.) = better performance of patients treated with risperidone |
| Brunnauer et al. (2004) | FGAs | Mean dose (CPA) | Schizophrenic and schizoaffective patients (n=120) | 18-59 | Other | PP |
|------------------------|------|-----------------|-----------------------------------------------|--------|-------|----|
| FGAs                   |      | 464,7mg         |                                               |        |       |    |
| SGAs                   |      | 535,2mg         |                                               |        |       |    |
| Flupenthixol           |      | 408.0mg         |                                               |        |       |    |
| Clozapine              |      | 528.6mg         |                                               |        |       |    |
|                        |      | (7 patients received biperiden comedication) |                                   |        |       |    |
|                        |      | Mean dose       |                                               |        |       |    |
|                        |      | 18-59           |                                               |        |       |    |
|                        |      | Other           |                                               |        |       |    |
|                        |      | PP              |                                               |        |       |    |
|                        |      | Mean dose       |                                               |        |       |    |
|                        |      | 5-30mg          |                                               |        |       |    |
|                        |      | 4-8mg           |                                               |        |       |    |
|                        |      | Schizophrenic and schizoaffective patients (n=40) | 33,1 (mean age) | 32,8 (mean age) | Other | PP |
|                        |      | (mean age)      |                                               |        |       |    |
|                        |      | Long-term treatment (n. spec.) = 27% severely impaired | | | |
|                        |      | Better performance of patients treated with SGAs (respectively clozapine) | | | |
| Brunnauer et al. (2005) | Haloperidol | Mean dose | Schizophrenic and schizoaffective patients (n=47) | 21-60 | Other | PP |
|                        | Flupenthixol | 6,3mg | | | | |
|                        | Risperidone | 5,5mg | | | | |
|                        | | 4,1mg | | | | |
|                        | (4 patients received biperiden comedication) | | | | | |
|                        | Haloperidol | Mean dose | Schizophrenic and schizoaffective patients (n=47) | 21-60 | Other | PP |
|                        | Flupenthixol | 6,3mg | | | | |
|                        | Risperidone | 5,5mg | | | | |
|                        | | 4,1mg | | | | |
|                        | (4 patients received biperiden comedication) | | | | | |
| Soyka et al. (2005) | Haloperidol | Mean dose | Schizophrenic and schizoaffective patients (n=40) | 33,1 (mean age) | 32,8 (mean age) | Other |
|                        | Risperidone | 5-30mg | | | | |
|                        | | 4-8mg | | | | |
|                        | (11 patients received biperiden comedication) | | | | | |
|                        | Haloperidol | Mean dose | Schizophrenic and schizoaffective patients (n=40) | 33,1 (mean age) | 32,8 (mean age) | Other |
|                        | Risperidone | 5-30mg | | | | |
|                        | | 4-8mg | | | | |
| Soyka et al. (2005) | Haloperidol | Mean dose | Schizophrenic and schizoaffective patients (n=40) | 33,1 (mean age) | 32,8 (mean age) | Other |
|                        | Risperidone | 5-30mg | | | | |
|                        | | 4-8mg | | | | |
| Soyka et al. (2005) | Haloperidol | Mean dose | Schizophrenic and schizoaffective patients (n=40) | 33,1 (mean age) | 32,8 (mean age) | Other |
|                        | Risperidone | 5-30mg | | | | |
|                        | | 4-8mg | | | | |
|                        | (11 patients received biperiden comedication) | | | | | |

- Long-term treatment (n. spec.) = 27% severely impaired
- Better performance of patients treated with SGAs (respectively clozapine)
- Long-term treatment (n. spec.) = 32% severely impaired
- Better performance of patients treated with risperidone
- Long-term treatment (n. spec.) = advantage for patients treated with risperidone in a risk-simulation
- Long-term treatment (n. spec.) = 42.5% of patients showed a very low performance
- Better performance of patients treated with risperidone
| Study | Medications | Dose | Patient Group | N | Outcome 1 | Outcome 2 | Outcome 3 |
|-------|-------------|------|---------------|---|-----------|-----------|-----------|
| Brunnauer et al. (2009) | Amisulpride, Quetiapine, Flupentixol, Haloperidol | 200-800mg, 300-800mg, 3-10mg, 2-15mg | Schizophrenic patients (n=80) | 18-60 | Other | PP | - Long-term treatment (n. spec.) = 27.5% severely impaired - Better performance of patients treated with amisulpride or quetiapine, especially in vigilance and concentration - Long-term treatment (n. spec.) = advantage for patients treated with amisulpride or quetiapine in a risk-simulation |
| Brunnauer and Laux (2012) | Sertindole, Risperidone, Quetiapine | 8-20mg, 2-8mg, 300-500mg | Schizophrenic patients (n=30) | 21-52 | Other | PP | - Long-term treatment (n. spec.) = 27% severely impaired - No significant differences between treatment groups |
| Treatment combinations | FGAs + comedication | n. spec. | Schizophrenic patients, manic depression, borderline (n=30) | 20-50 | Other | DS | - Subchronic and long-term treatment (n. spec.) = patients did not approach the level of healthy controls |
| Grübel-Mathyl (1987) | Combinations of FGAs neuroleptics, 7 on oral medication | 26 on depot medication | Schizophrenic and schizoaffective patients (n=33) | 20-44 | Other | PP | - Long-term treatment (n. spec.) = significant lower performance of patients when compared with healthy controls |
| Study                 | Drug Combinations                                      | Mean Dose | Patients | Other | PP            | Notes                                                                 |
|----------------------|--------------------------------------------------------|-----------|----------|-------|---------------|----------------------------------------------------------------------|
| Grabe et al. (1999)  | Haloperidol, Perazine, Chlorprothixene, Flupenthixol, Clozapine, Amisulpride + comedication | Mean dose | Schizophrenic patients (n=28) | 32,3 (mean age) | Other | PP            | Long-term treatment (n. spec.) = 32% severely impaired                |
|                      |                                                        | 9mg       |          |       |               | Significant better test performance of patients under polydrug treatment with clozapine in reactivity and stress-tolerance compared to FGAs |
| Kagerer et al. (2003) | Haloperidol, Amisulpride, Clozapine, Quetiapine, Risperidone, Olanzapine, Ziprasidone + comedication | Mean dose | Schizophrenic and schizoaffective patients (n=49) | 19-49 | Other | PP            | Long-term treatment (n. spec.) = 54% showed a very low performance with an advantage for patients treated with SGAs |
| Study                          | Drug/Comedication | Mean Dose | Patient Group | Age | Study Design | Other Notes                                                                 |
|-------------------------------|-------------------|-----------|---------------|-----|--------------|-----------------------------------------------------------------------------|
| Fuermaier et al. (2019)       | Antipsychotics +  | 8.7mg     | Schizophrenic patients (n=31) | 29.9 (mean age) | Other | DS | Long-term treatment (n. spec.) = patients drove slower than healthy controls; no indication of deviant driving |
| Veldhuijzen et al. (2006)     | Amitriptyline     | 25mg      | Chronic neuropathic pain patients (n=7) | 42-58 | RDBC ORT | Acute treatment (n) = impairment Subchronic treatment (n) = no impairment |
| Brunnauer et al. (2015)       | Agomelatine       | 25-50mg   | Depressive patients (n=20) | 50.4 (mean age) | RCT PP ORT | Subchronic treatment (n. spec.) = improvement Long-term treatment (n. spec.) = stabilization Depressed patients inferior to healthy controls Prior discharge depressed patients not significantly inferior to healthy controls |
| Brunnauer et al. (2008)       | Mirtazapine       | 30-60mg   | Depressive patients (n=20) | 25-67 | RCT PP ORT | Subchronic treatment (n. spec.) = improvement Depressed patients inferior to healthy controls Depressed patients
| Study                    | Treatment       | Dose     | Patient Group                  | Baseline Mean | Study Design | DS | Comparative to Controls |
|-------------------------|-----------------|----------|--------------------------------|---------------|--------------|---------|-------------------------|
| Shen et al. (2009)      | Mirtazapine     | 30mg     | Depressive patients (n=14)     | 29-67         | RCT          | DS      | not inferior to healthy controls |
| Brunauer et al. (2008)  | Reboxetine      | 2-8mg    | Depressive patients (n=20)     | 38-56         | RCT          | PP, DS  | subchronic treatment (n. spec.) = improvement |
| Roth et al. (2011)      | Trazodone       | 50mg     | Primary insomniacs (n=16)      | 18-65         | RDBC         | DS      | acute treatment (n) = no impairment (high drop-out rate) |
| Brunner et al. (2015)   | Venlafaxine     | 150-300mg| Depressive patients (n=20)     | 51.1 (mean age) | RCT          | PP, ORT | subchronic treatment (n. spec.) = improvement |

Comparative clinical studies
| Brunnauer et al. (2006) | Amitriptyline | 60-180mg | Depressive and bipolar patients (n=100) | 20-78 | Other | PP |
|------------------------|---------------|----------|---------------------------------------|-------|-------|----|
|                        | Doxepin       | 75-225mg |                                       |       |       |    |
|                        | Marprotiline  | 100-150mg|                                       |       |       |    |
|                        | Trimipramine  | 100-150mg|                                       |       |       |    |
|                        | Citalopram    | 20-40mg  |                                       |       |       |    |
|                        | Paroxetine    | 20-50mg  |                                       |       |       |    |
|                        | Mirtazapine   | 20-60mg  |                                       |       |       |    |
|                        | Venlafaxine   | 100-150mg|                                       |       |       |    |

| Wingen et al. (2006) | Citalopram    | 20-40mg  | Depressive patients (n=24) | 21-63 | Other | ORT |
|----------------------|---------------|----------|---------------------------|-------|-------|-----|
|                      | Paroxetine    | 20-40mg  |                           |       |       |     |
|                      | Sertraline    | 50-100mg |                           |       |       |     |
|                      | Venlafaxine   | 75-300mg |                           |       |       |     |

| van der Siulszen et al. (2017b) | Citalopram | 20-40mg | Depressive patients (n=65) | 21-63 | Other | ORT |
|---------------------------------|------------|--------|---------------------------|-------|-------|-----|
|                                 | Paroxetine | 20-40mg|                           |       |       |     |
|                                 | Sertraline | 50-100mg|                          |       |       |     |
|                                 | Venlafaxine| 75-300mg|                          |       |       |     |

**Treatment combinations**

- Long-term treatment (n. spec.) = 16% of patients showed severe impairment
- TCAs > SSRIs and Mirtazapine
- TCAs vs. Venlafaxine = no difference
- Mirtazapine < SSRIs

- Long-term treatment (n. spec.) = inferior to healthy controls
- No differences between treatment groups

- Long-term treatment (n. spec.) = better performance than untreated patients
- Untreated and treated patients inferior to healthy controls
|                  | Study Authors and Year | Antidepressant + Comedication | Patients (n) | Age (Range) | Other Treatments | DS                          | Notes                                                                 |
|------------------|------------------------|-------------------------------|-------------|-------------|-----------------|-----------------------------|----------------------------------------------------------------------|
| Hobi et al. (1981) | Tri- and tetracyclic antidepressants + comedication | n. spec. | Depressive and bipolar patients (n=31) | 20-50 | Other | DS | Subchronic and long-term treatment (n. spec.) = approached the level of healthy controls |
| Ramaekers et al. (1997) | Fluoxetine + BZD | 20-40mg | Depressive patients (n=17) | 18-32 | RDB | ORT | Long-term treatment (n. spec.) = impairment in patients with competitive benzodiazepine comedication at week 3 |
| Ramaekers et al. (1997) | Moclobemide + BZD | 300-600mg | Depressive patients (n=22) | 27-55 | RDB | ORT | Long-term treatment (n. spec.) = impairment in patients with a competitive benzodiazepine comedication |
### Table 1: Medication Use and Patient Characteristics

| Study: Grabe et al. (1998) | Amitriptyline | Desipramine | Trimipramine | Imipramine | Clomipramine | Maprotiline | Mianserin | Trazodone | Fluoxetine | Fluvoxamine | Paroxetine | Moclobemid | Tranylcypromine + comedication |
|---------------------------|---------------|-------------|--------------|------------|--------------|-------------|-----------|----------|-----------|------------|-----------|-----------|-----------------------------|
| Dosage: 125-250mg 100mg 100mg 150mg 150-300mg 100-150mg 30-50mg 150mg 20mg 100-200mg 30mg 300-600mg 20-30mg |
| Depressive patients: (n=44) | 44 (mean age) | Other | PP | |
| Characteristics: Long-term treatment (n. spec.) = 18% of patients showed severe impairment  No differences between treatment groups (TCAs, SSRIs, MAOIs) |
| Brunnauer and Laux (2003) | Amitriptyline | 60-180mg | Depressive patients (n=64) | 25-77 | Other | PP | Long-term treatment (n. spec.) = 20% of patients showed severe impairment | TCAs > selective antidepressants |
|--------------------------|----------------|----------|----------------------------|-------|-------|----|--------------------------------|----------------------------------|
|                          | Doxepin        | 75-225mg |                            |       |       |    |                                |                                  |
|                          | Citalopram     | 20-40mg  |                            |       |       |    |                                |                                  |
|                          | Fluoxetine     | 20-60mg  |                            |       |       |    |                                |                                  |
|                          | Fluvoxamine    | 150-300mg|                            |       |       |    |                                |                                  |
|                          | Paroxetine     | 20-40mg  |                            |       |       |    |                                |                                  |
|                          | Mirtazapine    | 20-60mg  |                            |       |       |    |                                |                                  |
|                          | Venlafaxine    | 150-375mg|                            |       |       |    |                                |                                  |
|                          | + comedication |          |                            |       |       |    |                                |                                  |
| Miyata et al. (2018)     | Antidepressants| n. spec.  | Depressive patients (n=65) | 24-57 | Other | DS | Long-term treatment (n. spec.) = not inferior to healthy controls with respect to driving performance |
|                          | + comedication |          |                            |       |       |    |                                |                                  |
van der Sluiszen et al. (2020)

| Treatment < 3 years | Patients (n=38) | 54,0 (mean age) | Other |
|---------------------|----------------|-----------------|-------|
| Amitriptyline       | 32,5 ± 29,0    |                 |       |
| Mirtazapine         | 22,0 ± 12      |                 |       |
| + comedication      |                |                 |       |
| Treatment > 3 years | 63,3 ± 52,7    |                 |       |
| Amitriptyline       | 26,7 ± 12,5    |                 |       |
| Mirtazapine         |                |                 |       |
| + comedication      |                |                 |       |

**Mood-Stabilizers**

**Comparative clinical studies**

| Study               | Drug      | Dosage          | Diagnoses          | Duration | Other | Long-term treatment (n. spec.) = impairment |
|---------------------|-----------|-----------------|--------------------|----------|-------|--------------------------------------------|
| Hatcher et al. (1990) | Lithium   | 400-1250mg      | Bipolar (n=16)     | 18-63    | Other | Long-term treatment (n. spec.) = no impairment in all antidepressant users |
| Jauhar et al. (1993)  | Lithium   | Serum Level 0,5 - 1,5 mmol/l | Bipolar and unipolar (n=20) | 45 (mean age) | Other | Long-term treatment (n. spec.) = impairment when treated < 3 years |
|            | Lithium | Lamotrigine | 600-1000mg | Bipolar (n=24) | 25-63 | Other | PP |            |
|------------|---------|-------------|------------|----------------|-------|-------|----|------------|
|            |         |             | 200-400mg  |                |       |       |    | Long-term term (n. spec.) = 17% of patients severely impaired |
|            |         |             |            |                |       |       |    | Better test performance of patients treated with lamotrigine |

**Benzodiazepines**

**Tranquilizer**

|            | Diazepam | 15mg | Generalized anxiety disorder (n = 12) | 18-50 | DBC | ORT |            |
|------------|----------|------|--------------------------------------|-------|-----|-----|------------|
|            |          |      |                                      |       |     |     | Acute treatment (d) = impairment |
|            |          |      |                                      |       |     |     | Subchronic treatment (d) = impairment |
|            |          |      |                                      |       |     |     | Long-term treatment (d) = no impairment |

|            | Medazepam | 5 - 30mg | Anxiety patients (n = 14) | 20-40 | DBC | SORT |            |
|------------|-----------|----------|--------------------------|-------|-----|------|------------|
|            |           |          |                          |       |     | DS   | Subchronic treatment (d) = impairment |
|            |           |          |                          |       |     |      | Subchronic treatment (d) = no impairment |

**Hypnotics**

|            | Flunitrazepam | 2mg | Insomniacs (n = 16) | n. spec. | RDB | ORT |            |
|------------|---------------|-----|---------------------|----------|-----|-----|------------|
|            |               |     |                      |          |     |     | Acute treatment (n) = impairment |

| van Laar et al. (1992) | Moore (1977) | Schmidt et al. (1986) | Diazepam | Medazepam | Flunitrazepam |
|------------------------|--------------|-----------------------|-----------|-----------|--------------|
| 15mg                   | 5 - 30mg     | 2mg                   | Generalized anxiety disorder | Anxiety patients | Insomniacs |
| Generalized anxiety disorder (n = 12) | Anxiety patients (n = 14) | Insomniacs (n = 16) | 18-50 | 20-40 | n. spec. | |
| 18-50                   | 20-40        | n. spec.              |            |           |              | |
| Study               | Drug      | Dose (mg) | Condition      | Age Range | Measure | Effect |
|---------------------|-----------|-----------|----------------|-----------|---------|--------|
| Vermeeren et al. (1995) | Flunitrazepam | 2mg | Insomniacs (n = 17) | 25-51 | DBC | **Acute treatment (n) = no impairment** |
| Brookhuis et al. (1990) | Flurazepam | 30mg | Insomniacs (n = 16) | 26-41 | DBC | **Acute treatment (n) = impairment** |
| Brookhuis et al. (1990) | Lormetazepam | 1/2mg | Insomniacs (n = 32) | 26-41 | DBC | **Acute treatment (n) = no impairment** |
|                     |           |          |                |           |        | Acute treatment (n) = impairment (1mg) |
|                     |           |          |                |           |        | no residual effect was found in the afternoon |
| Staner et al. (2005) | Lormetazepam | 1mg | Insomniacs (n = 23) | 38.8 (mean age) | RDBC | DS | **Acute treatment (n) = impairment** |
| Partinen et al. (2003) | Temazepam | 20mg | Insomniacs (n = 18) | 35-58 | RDBC | DS | **Acute treatment (n) = no impairment** |
| Schmidt et al. (1986) | Temazepam | 20mg | Insomniacs (n = 16) | n. spec. | RDB | ORT | **Acute treatment (n) = no impairment** |

**Z-drugs**
| Study                | Drug   | Dose  | Condition                    | Age     | Measure | Effect                   | Notes                                                                 |
|---------------------|--------|-------|------------------------------|---------|---------|--------------------------|----------------------------------------------------------------------|
| Partinen et al. (2003) | Zolpidem | 10mg  | Insomniacs (n = 35-58)       | RDBC    | DS      | Acute treatment (n)      | no impairment                                                        |
| Staner et al. (2005)  | Zolpidem | 10mg  | Insomniacs (n = 38.8)        | RDBC    | DS      | Acute treatment (n)      | no impairment                                                        |
| Vermeeren et al. (1995) | Zolpidem | 10mg  | Insomniacs (n=17)            | DBC     | ORT     | Acute treatment (n)      | no impairment                                                        |
| Leufkens et al. (2014a) | Zopiclone | 7.5mg | Insomniacs (n=32)            | DBC     | ORT     | Acute treatment (n)      | impairment                                                             |
|                      |        |       |                              |         |         | The magnitude of         | impairment was significantly less in the chronic hypnotic users group |
| Staner et al. (2005)  | Zopiclone | 7.5mg | Insomniacs (n = 38.8)        | RDBC    | DS      | Acute treatment (n)      | impairment                                                            |

**Comparative clinical studies (hypnotics)**
| Treatment combinations | Zopiclone | Temazepam | Midazolam | Oxazepam | Zolpidem | Lormetazepam | Loprazolam | Clonazepam | Flurazepam | Nitrazepam | n.spec. | Insomniacs (n = 42) | 50-75 | Other | ORT | Long-term treatment (n. spec.) = no difference between frequent or infrequent users and healthy controls |
|------------------------|----------|-----------|-----------|----------|----------|-------------|------------|------------|-----------|-----------|--------|---------------------|-------|-------|-----|------------------------------------------------|
|                        | Leufkens et al. (2014b) |           |           |           |          |              |            |            |           |           |        |                     |       |       |     |
| van der Sluiszen et al. (2019) | Alprazolam | Bromazepam | Brotizolam | Diazepam | Lorazepam | Lormetazepam | Midazolam | Nitrazipam | Oxazepam | Temazepam | Zolpidem | Zopiclone |
|-------------------------------|------------|------------|------------|----------|-----------|--------------|-----------|------------|----------|-----------|----------|----------|
| n. spec.                      | Patients (n = 44) | Hypnotic group: 55.6y (mean age) | Other | ORT | ➢ Long-term treatment (n. spec.) = impairment with hypnotics (treatment < 3 years and > 6 month) | ➢ Long-term treatment (n. spec.) = no impairment with hypnotics (treatment > 3 years) | ➢ Long-term treatment (n. spec.) = no impairment with anxiolytics |
| + comedication | | | | | | | | | | | | |

Note: *Outcome: acute = day 1-7, subchronic = day 8-21, Long-term >21 days; (d) = during the day (i.e. dosages were given at the day of driving assessment); (n) = nocturnal (i.e. dosages were given in the night before driving assessment); (n. spec.) = not specified; CPÅ = chlorpromazine-equivalents; Aps = antipsychotics; BZDs = benzodiazepines; FGAs = first generation antipsychotics; SGAs = second generation antipsychotics

PP = psychomotor performance; ORT = on-road-test; SORT = simulated on-road-test; DS = driving simulator

Other = cross-sectional or open label study; RDBC = randomized double blind crossover; DBC = double blind crossover; RDB = randomized double blind; RCT = randomized clinical trial.
Table 2: Summary of results of controlled experimental patient studies on monotherapy with antipsychotics, antidepressants, mood-stabilizers, benzodiazepines and Z-drugs on driving performance

| Substance         | No. of investigations | Acute effects* | Subchronic-/long-term-effects* | Checked doses (mg) | Therapeutic range (mg) |
|-------------------|-----------------------|----------------|-------------------------------|--------------------|------------------------|
| **Antipsychotics** – no data available |                       |                |                               |                    |                        |
| **Antidepressants** |                       |                |                               |                    |                        |
| Amitriptyline     | 1                     | ↓              | ↔                             | 25                 | 50-225                 |
| Agomelatine       | 1                     | ----           | ↑                             | 25-50              | 25-50                  |
| Mirtazapine       | 2                     | ↑              | ↑                             | 30-60              | 15-45                  |
| Reboxetine        | 1                     | ---            | ↑                             | 2-8                | 4-10                   |
| Trazodone         | 1                     | ↔              | ---                           | 50                 | 150-600                |
| (high drop out rate) |                       |                |                               |                    |                        |
| Venlafaxine       | 1                     | ---            | ↑                             | 150-300            | 75-375                 |
| **MAO-inhibitors** – no data available |                       |                |                               |                    |                        |
| **Mood stabilizers** – no data available |                       |                |                               |                    |                        |
| **Benzodiazepines** - tranquilizers |                       |                |                               |                    |                        |
| Diazepam          | 1                     | ↓              | (until week 3)                | 15                 | 5-20                   |
|                   |                       |                | (after week 3)                |                    |                        |
| Medazepam         | 1                     | ---            | ( )                           | 5-30               | 10-30                  |
| Drug               | Benzodiazepines – hypnotics | Z-drugs       |
|--------------------|-----------------------------|---------------|
| Flunitrazepam      | 2 ( ) , 1 ( ) , ---        | --- 20,5-1    |
| Flurazepam         | 1 ↓ , ---                    | 30 15-30      |
| Lormetazepam       | 2 ↓ 1mg ( ), ---            | 1/2 0,5-2     |
| Temazepam          | 2 ↔ , ---                    | 20 10-40      |
| Zolpidem           | 3 ↔                         | --- 10 5-10   |
| Zopiclone          | 2 ↓ , ---                    | 7,5 3,75-7,5  |

--- = no data available; ( ) = inconsistent data; ↔ = no impairment; ↓ = impairment; ↑ = improvement;

*Treatment effects: acute = day 1-7, subchronic = day 8-21, long-term >21 days.
Figure 1

Identification

1417 records identified through systematic database searching; Limits: English and German language articles only

Screening

1275 records excluded on a title and abstract level (e.g. no patient studies, epidemiologic studies, reviews, duplicates)

Eligibility

142 full-text articles assessed for eligibility

103 articles excluded on this full-text level, not meeting methodological constraints

Included

40 studies included for a qualitative synthesis

1 additional record identified through other sources (personal communication)