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Review

Mirtazapine as positive control drug in studies examining the effects of antidepressants on driving ability

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ABSTRACT

The development of effective and safe antidepressant medications is ongoing, and driving studies are critical to assess a drug's safety. The current review summarizes the effects of a sedating effective antidepressant, mirtazapine, on driving ability, and its potential to serve as positive control drug in future driving studies. Three on-road driving studies and four driving simulator studies of mirtazapine were identified. The studies, conducted in healthy volunteers, showed a significant dose-dependent driving impairment, the first day following bedtime administration of mirtazapine. The magnitude of impairment after a single dose of 15 mg or 30 mg mirtazapine was comparable to that observed with a blood alcohol concentration of 0.05%, the legal limit for driving in many countries. After 1 or 2 weeks of daily treatment with mirtazapine, partial tolerance developed to mirtazapine's effects on driving. Driving studies conducted in patients were less informative, as the effect on driving caused by mirtazapine was obscured by a drug–disease interaction and increased variability in patient groups. In conclusion, mirtazapine is useful as positive control drug to assess the potential effects of new antidepressant drugs on driving. Studies in normal healthy volunteers are more sensitive to drug effects than studies in patient populations.

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1. Introduction

Depression is a common psychiatric disorder with an estimated life time prevalence of around 15% (Bromet et al., 2011). Patients who suffer from depression are often treated with antidepressant drugs such as tri-cyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). Unfortunately, antidepressant drugs can have side effects that impair cognitive functioning and alertness. Most of those who use antidepressants are outpatients and therefore it is likely that they drive. This is of concern, as driving studies have shown that even after long-term treatment with SSRIs, driving in patients with depression was significantly worse than that of matched healthy controls (Wingen et al., 2006). This may in part

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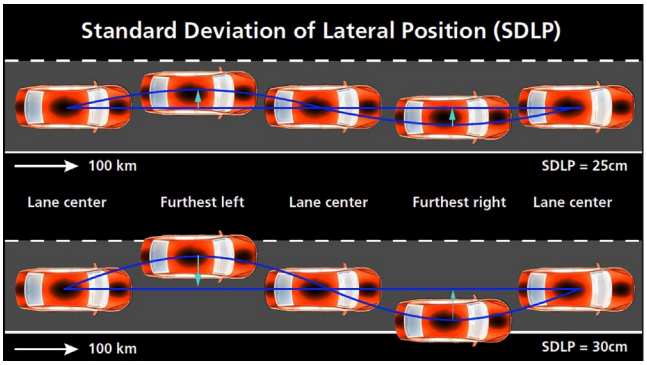

Fig. 1. Standard Deviation of Lateral Position (SDLP).

be due to the fact that even with long-term treatment patients may not be fully free from depressive symptoms. On the other hand, adverse drug effects may persist having an impact on alertness and other aspects of daytime functioning. The development of safer antidepressant drugs is therefore ongoing. As driving includes risk of accidents, injury or even death, potential driving impairment due to possible adverse drug effects is a relevant issue for patients who need to use antidepressants. Driving studies are therefore critical when assessing a drug's safety profile.

Driving is a complex activity involving a wide range of cognitive, motivational perceptual, and motor activities. More importantly, driving is the interaction of all these skills. Measuring them separately is of academic interest, but does not address effects on driving per se (which require their integration). Validation studies have shown that psychomotor test performance is a poor predictor of actual driving performance (SDLP) (Ramaekers, 2003; Verster and Roth, 2012), nor has it been shown that performance on these tests predict driving accidents. Although it may be of scientific interest to examine which skills and abilities are related to driving, or how the medication impacts these skills, for patients the only relevant question is whether driving is impaired by the drug, and if so how much compared to a calibrated standard (i.e. alcohol).

Currently, the standardized on-the-road driving test is the gold standard to assess driving safety (Verster and Roth, 2011). The on-the-road driving test was developed in the 1980s to objectively determine driving ability in a real life setting (O'Hanlon et al., 1982). In the 100 km driving test, subjects are instructed to operate an instrumented vehicle with a constant speed and steady lateral position within the right (slower) traffic lane. Primary outcome measure is the Standard Deviation of Lateral Position (SDLP), i.e. the amount of weaving of the car (see Fig. 1) (Verster and Roth, 2011).

Other outcome measures include the standard deviation (SD) of speed, out of lane deviations, and number of lapses. Mean lateral position and mean speed are control variables. Over the past 30 years, the standardized driving test was used to demonstrate dose-dependent increment of SDLP (relative to placebo) for alcohol, and a variety sedative hypnotics, anxiolytics, antidepressants and antihistamines (Verster and Mets, 2009; Penning et al., 2010), but also driving improvement has been demonstrated using this methodology with a variety of substances (Verster et al., 2008). SDLP is a stable measure within subjects, but highly variable between subjects (Verster and Roth, 2011). Therefore, driving studies are usually designed as crossover studies in which all subjects receive all treatments, with a placebo condition and typically an active control as reference. As a cut off value for clinical relevant SDLP increments relative to the placebo, usually an increment of +2.4 cm is chosen, as this was found after administering alcohol to achieve a blood alcohol concentration of 0.05% (Louwerens et al., 1987), i.e. the most common legal limit for driving a car.

In addition to the cut-off point of clinical relevance, in a clinical trial it is important to establish assay sensitivity. This is typically achieved by including a positive control in the design. As the sole purpose of this drug is to show impairment at a clinically relevant level, the drug class to which it belongs is therefore not critical. Nevertheless, positive control drugs are often sought among drugs for the same treatment of the drug under investigation, because comparable adverse effect profiles facilitate blinding of the treatments. For example, when testing the next-morning effect of hypnotics on driving, zopiclone 7.5 mg is often used as positive control drug (Verster et al., 2011). Although it may be tempting to argue that alcohol is the most appropriate positive control because its impairing effect on driving is better characterized than for any other potential positive control, this is not correct. Including alcohol as positive control will result in problems with proper blinding of the treatments, as many people who have consumed alcohol are familiar with feelings of intoxication. Therefore, alcohol can better be replaced by another drug (unknown to participants) that does have an impairing effect on driving.

In studies examining the potential adverse effects of antidepressants on driving, mirtazapine is often used as positive control drug. The antidepressant properties of mirtazapine are linked to the drug's antagonist action at the α_2-adrenoceptor, 5-HT_2 and 5-HT_3 serotonergic receptors, and histamine (H_1) receptor (Nutt, 2002). Its affinity for H_1 and 5-HT_2 receptors likely explains its sedative effects and usefulness in depressive patients who also suffer from sleep problems. Mirtazapine is normally prescribed in dosages ranging from 15 mg to 45 mg, and orally administered at bedtime. The half-life of mirtazapine is 20–40 h and peak plasma concentrations are reached within 2 h after oral administration.

The purpose of this review is to summarize the available scientific data on the effects of mirtazapine on driving ability, and to determine its usefulness as positive control.

2. Materials and methods

A literature search on PubMed was performed (September 5th, 2014) using the keywords "mirtazapine" and "driving". This yielded 13 Articles which were evaluated. In addition, cross-references were checked. Studies were included if mirtazapine's effects on driving were assessed using the on-the-road driving test or a driving simulator. Seven studies met these criteria and were included in this review.

3. Results

3.1. Driving studies in healthy volunteers

Three double blind placebo controlled crossover studies used on-the-road driving testing to examine the effects of mirtazapine on driving ability. In these studies, mirtazapine was self-administered at bedtime and highway driving tests were conducted the following morning. In the first study, $N=18$ healthy volunteers used mirtazapine 15 mg for 7 nights, followed by another week with bedtime administration of mirtazapine 30 mg (Ramaekers et al., 1998). Driving tests were conducted on day 2 (next morning effects after a single bedtime dose of mirtazapine 15 mg), day 8 (steady-state effects after 7 nights of mirtazapine 15 mg), day 9 (after dose escalation to mirtazapine 30 mg), and day 16 (steady-state effects of mirtazapine 30 mg). The driving test was conducted 17–18 h after treatment administration. Relative to placebo, a significant increase in SDLP was found on day 2 (ΔSDLP = +2.2 cm), but not after sub-chronic use of mirtazapine 15 mg (day 8), and the day after dose escalation (day 9). Significant driving impairment was however found after sub-