Effects of dextromethorphan, temazepam and ethanol on human performance

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Background

CNS-depressant drugs act on a variety of receptors, including NMDA and GABA. Ketamine is most often used as an NMDA antagonist, but there are potential problems in human volunteer studies due to its ability to induce psychotic symptoms.

Dextromethorphan (DX) is a possible alternative. As a low-affinity NMDA antagonist it may have a higher therapeutic margin than ketamine. It is used in low doses in over-the-counter cough medicines, and in higher doses for pain management (1). However it has seldom been used in this type of volunteer study (2).

We have explored the use of this compound in psychopharmacology, comparing the effects of DX on cognitive function with two drugs whose effects are well-established, ethanol and temazepam.

The Study

We used a five-period crossover design, comparing:

- Placebo
- Ethanol (target BAC 90 mg/100 ml)
- Temazepam 30 mg
- DX 150 mg
- DX 250 mg

Treatment order was determined using a constrained randomisation, so that the low dose of dextromethorphan always preceded the higher dose. Tests of attention, memory and psychomotor performance were carried out before the dose and over the next 3 h, as well as Visual Analogue Scales (VAS) to assess subjective effects

Fifteen volunteers (9 males and 6 females) aged 18-23 years (mean 20.6) and weighing 54-91 kg (mean 71.3) took part. All were extensive metabolisers of dextromethorphan as assessed by a prior phenotyping session.

Adverse Events with Dextromethorphan

Seven volunteers received DX. Three of these had significant adverse events on the low dose which interfered with test procedures, including nausea, vomiting and dizziness. One withdrew from the study, and the DX arm was discontinued after 7 had received the low dose and 1 the high dose. All seven volunteers reported subjective effects of DX, including feeling drunk, light-headed, or disinhibited.

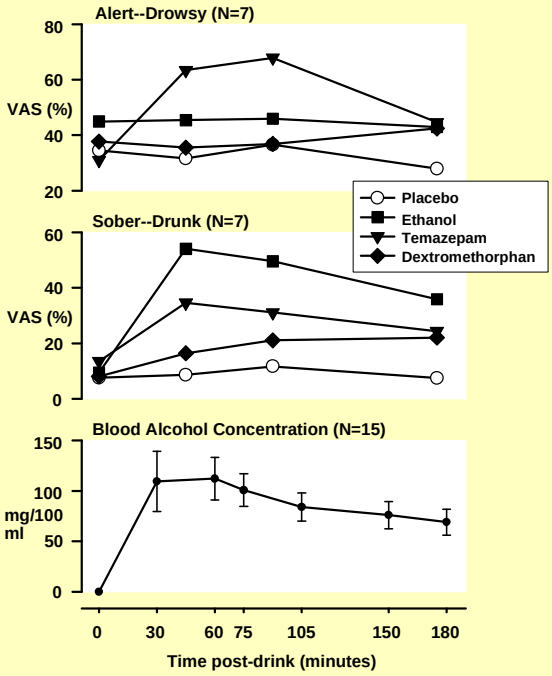
These effects came on suddenly, usually at about 60-90 minutes post-dose, and persisted for two or three hours, leaving the volunteer feeling “spaced-out”. Effects generally wore off completely after about eight hours post-dose.

Paired-Associate Learning. Two shapes appear, one on the left, the other on the right of the screen

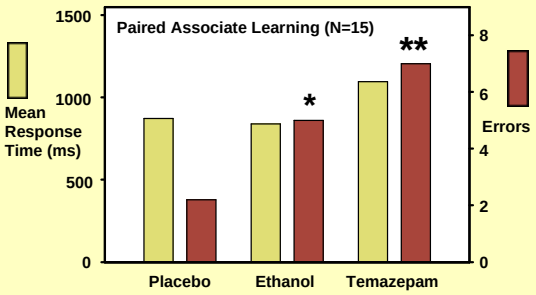
Then single shapes appear. The volunteer presses the Left or Right button to indicate on which side the shape originally appeared.

Results

Little effect on mood or performance was seen with dextromethorphan. Results for the subjective VAS are shown below, and indicate slight but not significant feelings of drunkenness with the 150 mg dose. No objective test showed evidence of impairment with DX



By contrast, ethanol and temazepam showed the expected effects on the objective and subjective measures used. For example Paired Associates showed impairment with both drugs



Conclusions

1. Dextromethorphan is not sufficiently well-tolerated to be suitable for assessing the role of NMDA in human cognition
2. Its subjective effects are consistent with those of other NMDA receptor antagonists
3. Ethanol and temazepam had the expected effects on function, impairing the speed and accuracy of performance.

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References.

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