

## ST and Reversible MAOIs (RIMAs)

### Moclobemide

#### Abstract

Therapeutic doses of Moclobemide combined with any (S)SRI carries a significant risk of potentially fatal serotonin toxicity. This is unpredictable when multiple pharmacokinetic interactions via P-450 come into play.

#### Introduction

Moclobemide does confer a risk of serotonin toxicity with (S)SRIs although the history and evidence relating to its interactions is clouded with misleading information put out by the drug company. Although this drug is infrequently used because of its low therapeutic efficacy — there seems to be widespread appreciation of the view I espoused decades ago, which is that moclobemide is of minimal effectiveness as an anti-depressant drug. Indeed, I have stated on more than one occasion that those of my colleagues who thought it was a generally effective antidepressant for severe depression neither understood depression nor how to treat it.

I will re-post the detailed analysis about moclobemide & ST separately at some later date, because the original section in the serotonin toxicity document posted years ago needs tidying up and re-referencing and because it is of ‘historical’ interest to some researchers.

Suffice it to say that even at therapeutic doses, and most definitely following overdoses [1, 2], one can get severe serotonin toxicity interactions with SRIs, and deaths have occurred. I summed it up more than ten years ago in this brief comment [3] in a way which I have not since **bettered\***:

**There is not much room for debate about this, it is an unpredictably dangerous interaction**

A discussion that was brought to my attention from an Internet site — it may be educative to pick a few statements from this thread to illustrate how great the danger is of a little knowledge. As Jagger said, ‘don’t play with me ‘cos you’re playing with fire’.

<http://www.socialanxietysupport.com/forum/f30/moclobemide-ssri-combination-1367249/>

An opening comment is ‘This forum is interesting with the amount of information & knowledgeable people here.’

**However, the knowledge this correspondent refers to is a simulacrum of knowledge and expertise, not the real thing**

Remember what Shaw said [4] ‘*Beware of false knowledge; it is more dangerous than ignorance.*’ The problem for many readers of such forums is the difficulty of distinguishing between real and false knowledge. It is a problem for all of us, but especially for the less informed, because ignorance cannot to recognize itself in the mirror.

At this point I will refrain from a tirade about Facebook, Twitter, twerp and twaddle, as I call them.

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\* ... moclobemide/SRI combinations represent a predictably risky strategy and constitute a balancing act, between efficacy and fatality, of such delicacy as to be unattainable in clinical practice

Just look up the meaning of the word *ultracrepidarian*

My personal experience with this was very positive with 20mg Fluoxetine and 150mg Moclobemide. Fluoxetine increases blood levels of Moclobemide so low doses can be used, even though the studies use dosages up to 600mg.

I will not beat about the bush. The doctor supervising the treatment this person reports is putting himself in significant danger of a) being successfully sued by the family, should the patient be unfortunate enough to die, or worse, suffer severe permanent morbidity, b) as well as being in danger of being struck off the medical register.

### *Interactions*

Moclobemide levels are increased by inhibition of CYP450 2C19 and Moclobemide itself inhibits P450 2D6 [5-10]. Some of the SSRIs with which people have tried to combine it, also inhibit its, and their own, metabolism. That creates a positive feedback-cycle of a problematic nature. My experience indicates that most psychiatrists have an insufficient knowledge of these matters to enable them to manage any such combinations safely.

I am prepared to wager a considerable sum that few psychiatrists would be able to give an accurate précis of the data I summarise here.

There is no doubt that a therapeutic level of any SRI combined with a high therapeutic level, or small overdose, of moclobemide is capable of inducing fatal serotonin toxicity

The combination of Fluoxetine/Moclobemide is a perfect storm looming on the horizon.

Blood levels of moclobemide can be altered by inhibition of P-450 2C19, to an extent comparable to the levels expected with a small overdose [1]. It is therefore obvious that in some individuals small changes of dose of a drug that inhibits P450 could alter blood levels enough to precipitate ST in someone who previously appeared well and without problems on their previous dosage.

This scenario is an example of what I said above which is '*a little knowledge is a dangerous thing*' and unfortunately this doctor and his patient are in the category of those who have insufficient knowledge.

Fluoxetine is the worst possible choice for an SSRI to combine with moclobemide (fluvoxamine comes a close second) because it is a potent inhibitor of several cytochrome P-450 enzymes including 2C19, which are responsible for metabolizing moclobemide. In such situations potently inhibiting these enzymes can increase blood levels of drug to the equivalent of those in persons who have taken a small overdose. The situation may be further complicated by other drugs in the patient's regime which affect blood levels of either fluoxetine or moclobemide, because, in this instance, not only will Fluoxetine inhibit moclobemide metabolism but also moclobemide will also inhibit the metabolism of fluoxetine making it a two-way street. Any other drug which raises blood levels of either fluoxetine or moclobemide (of which there are plenty) can potentially start the snowball rolling.

The chess-like complexity of this situation is yet further magnified by the fact that fluoxetine inhibits its own metabolism and has an elimination half-life of up to 10 days, thus blood levels can unexpectedly elevate because of small changes in absorption etc. A double dose taken by mistake and various other circumstances might easily lead to a fluoxetine level that unexpectedly becomes considerably higher than usual which might in turn elevate moclobemide.

Such a combination is akin to holding a hand grenade with the pin taken out, when you cannot count

The ‘personal experience’ mentioned in the forum above of one individual (probably over a short period of time) is unhelpful and misleading for the general ‘unscientific’ reader.

Someone else stated

**You will find multiple papers endorsing this combination, the mainstream view is its dangerous, which is misinformed.**

Leaving aside the extra-ordinary hubris of this ill-informed contributor — definitely classifiable as ultracrepidarian — I trust readers with more understanding of scientific research and literature will appreciate that this is a dangerous and unhelpful statement. First, it is incorrect. There are only a small number of papers with small numbers of patients claiming that this treatment is helpful and safe [11-15]\*

Another commentator hit the nail on the head when he pointed out that these papers were published 20 years ago and have never subsequently been followed up. A cautious enquirer would want to know why these researchers failed to capitalize on this ‘successful’ breakthrough that would have enhanced their reputation and career. This is because the doctors concerned encountered serious problems which they did not report, but which discouraged their efforts and ethical committees probably (and rightly) vetoed further efforts.

Since those reports, I have corresponded with the relevant researchers, some of whom failed to respond to enquiries about difficulties, others revealed they had difficulties. I know of no research center that has done work with this combination since then.

It is not possible to state that some such combination might not be useful, it might be. However, it is clear that practitioners who have dabbled in this area do not know enough about pharmaco-kinetics, pharmaco-dynamics or ST to experiment safely. I suspect a lot of ethics committees have agreed with that.

Do not forget that the early work, where fluoxetine was combined with SRIs, lead to a number of deaths, which were only published some years later [16]. It is clear those researchers had little idea of the pharmacology, or the danger to which they were exposing those research subjects.

I also note one particular curious comment about avoiding this combination in patients who are suicidal. Patients who are potentially going to become suicidal are the only candidates for this sort of treatment because serious endogenous depression, for which such combinations would be the only justifiable indication, may lead periodically to worsening which is likely to entail suicidal thoughts and intent. That fact makes the argument illogical especially because suicidal thoughts and intent are difficult both to assess and predict.

## References

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\* One of these authors, Chris Hawley, laughed at me when I told him at a conference meeting that he was skating on thin ice — I warned him he would need a couple of pairs of brown trousers. When I met him a year or two later, he rather sheepishly confided he had aborted such trials. One of the patients nearly died and I pressured him to write up the case for publication. He sent me a draft of his right up, because I had offered to assist him to get it published, but then his enthusiasm waned, and it was never published. I wondered if he had got himself into ethical or medico legal trouble as a result of that case. Either way, he went quiet, stopped replying to messages, and I never heard from him again.

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