

Triptans and SSRI or SNRI antidepressants – is there an interaction?

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Background

Triptans and selective serotonin/noradrenaline re-uptake inhibitors (SSRIs/SNRIs) are commonly used to treat migraine and depression, respectively. As migraine and depression often occur together, there is significant potential to co-prescribe these agents (1). Both triptans and SSRIs/SNRIs have serotonergic activity; triptans are serotonin agonists and SSRIs/SNRIs inhibit active re-uptake of serotonin. In 2006 the US Food and Drug Administration (FDA) issued an alert warning of potentially life-threatening consequences when triptans and SSRIs/SNRIs are used concomitantly (2).

The likelihood of an interaction between triptans and SSRIs/SNRIs resulting in serotonin syndrome is considered in this Medicines Q&A.

Further background information on serotonin syndrome can be found in the UKMi Q&A [What is serotonin syndrome and which medicines cause it?](#)

Answer

Mechanisms of the potential interaction

The interaction between triptans and SSRIs/SNRIs is thought to result from both pharmacodynamic and pharmacokinetic mechanisms.

The basis of the pharmacodynamic interaction is an additive effect on the serotonergic system. However, the premise for this has been challenged (3). It is believed that serotonin syndrome primarily occurs through activation of 5-hydroxytryptamine 2A (5HT_{2A}) receptors, although 5HT_{1A} receptors may also have a role (1). Triptans are agonists at 5HT_{1B/1D/1F} receptors, with weak affinity for the 5HT_{1A} subtype, and no activity at 5HT₂ (1). Consequently, triptans should not increase the risk of serotonin syndrome. However, a review of the FDA's Adverse Event Reporting System (AERS) up to 2008 identified 11 possible cases associated with triptan monotherapy; three cases were reported as serotonin syndrome and eight described symptoms indicative of the syndrome (4). A subsequent review of AERS in 2012 identified an additional 20 possible cases, but it is unclear whether these reports were associated with triptan monotherapy (5). The usual caveats relating to such reports apply. In contrast, based on their mechanism of action, SSRI monotherapy would be expected to be associated with serotonin syndrome and estimates suggest an incidence of 0.5 to 0.9 cases per 1,000 patient-months of treatment (3).

Potential pharmacokinetic interactions arise as SSRIs/SNRIs inhibit cytochrome (CYP) P450 isoenzymes: citalopram, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine and duloxetine inhibit CYP2D6 and fluvoxamine inhibits CYP1A₂, 2C₉, 2C₁₉ and 3A₄, in addition to CYP2D6 (6-13). These isoenzymes are involved in metabolising a number of triptans. One study in 14 healthy subjects found that fluoxetine raised the maximum plasma level (C_{max}) of almotriptan by about 18% (14). Similarly, fluvoxamine increased frovatriptan C_{max} levels by approximately 28% in 16 volunteers (15). However, in both studies dose adjustment was considered unnecessary. The results of three further small pharmacokinetic studies in healthy volunteers found concurrent administration of sumatriptan and paroxetine (n=11), zolmitriptan and fluoxetine (n=16) and rizatriptan and paroxetine (n=12) did not alter triptan plasma levels (16-18).

Evidence suggesting an interaction in clinical practice

A small number of published reports describe symptoms of serotonin syndrome following concomitant use of a triptan and an SSRI. A 65-year-old woman who had been taking paroxetine 20mg/day for a number of years developed confusion, sinus tachycardia and hyperthermia shortly after starting sumatriptan (16). She recovered on drug withdrawal. A 28-year-old woman on fluoxetine 60mg daily for one year, eletriptan 40mg for six months (taking three to four times a month) and St John's wort for one month was admitted to hospital with loss of consciousness followed by seizures with confusion and, after several days, suspected rhabdomyolysis. In the three days before admission she had taken eletriptan 40mg daily to treat recurrent migraine (19). A 14-year-old girl who had been taking fluoxetine for one year, became confused and drowsy within two days of starting rizatriptan, amitriptyline and topiramate for worsening headaches. She had a prolonged seizure on the third day and required intubation (20).

A review, which included published case reports and unpublished reports to pharmaceutical manufacturers and regulatory agencies, identified 16 cases of symptoms suggestive of serotonin syndrome when sumatriptan was used with fluoxetine or sertraline (21). Details of the reaction were given in three cases. A woman taking sertraline, lithium and methysergide (a serotonin antagonist) developed sudden onset weakness, loss of co-ordination and abnormal jerking within one hour of receiving sumatriptan 6mg subcutaneously. Similar but less severe episodes occurred with subsequent doses of sumatriptan after lithium was discontinued, but not once sertraline was stopped. A patient taking sertraline and propranolol became anxious, agitated, disorientated, weak and tachycardic after subcutaneous sumatriptan. These symptoms did not recur when nortriptyline was substituted for sertraline. In the third case, a 29-year-old woman treated with fluoxetine 30mg daily for over two years for depression, experienced clamminess, nausea and insomnia within one hour of taking 100mg sumatriptan orally. A second dose of sumatriptan the next day resulted in sweating, restlessness and features consistent with a panic attack. These symptoms resolved without treatment.

Post-marketing surveillance of voluntary reports received in Canada by the manufacturer of fluoxetine identified two cases that showed good evidence, and four cases that showed modest evidence, of serotonin syndrome with sumatriptan (16).

The 2006 FDA alert was issued following a review of 27 cases of possible serotonin syndrome reported to AERS, 13 of which required hospitalisation with two involving life-threatening events (2). A number of cases occurred in patients who had previously used the combination of SSRI/SNRI and triptan without relevant adverse outcome. In eight cases, recent dose increases or addition of another serotonergic drug to the combination were related to symptom onset; in these cases, median time to onset was one day, with a range of ten minutes to six days. The FDA requested that all manufacturers of triptans, SSRIs and SNRIs update their prescribing information to warn of a possible interaction. At the time, the agency noted that the warning was based on preliminary analysis of data and that the recommendations would be reviewed when additional information became available (22). As of December 2018, an update has not been issued and the original alert has been archived on the FDA website. An independent analysis (22) of the original 27 FDA cases, plus two additional cases, found that only seven [later revised to ten (23)] of the 29 cases met the Sternbach criteria for a diagnosis of serotonin syndrome and none met the more rigorous Hunter criteria (1). The reviewer concluded that the information does not warrant prohibiting the use of triptans with SSRIs/SNRIs (22).

Evidence against an interaction in clinical practice

Evidence of safety for concomitant use of triptans and SSRIs comes from several studies. A large prospective study followed 12,339 patients who used subcutaneous sumatriptan for migraine for up to one year; 1,784 (14.5%) of these patients also took an SSRI during the study. There was no increase in reports of adverse effects within 24 hours of administering sumatriptan (24). In addition, during the clinical development programme for sumatriptan (oral and subcutaneous), 48 of 806 patients received an SSRI concurrently without adverse consequence (25). In a small uncontrolled prospective study, none of 12 patients receiving SSRIs experienced any significant side effects when they took oral sumatriptan on a total of 91 occasions (26). A further six patients were reported to have used sumatriptan concurrently with an SSRI without apparent adverse effects for periods of up to 18 months (25). No adverse effects that suggested serotonin syndrome were observed with

combinations of fluoxetine and zolmitriptan (17) and paroxetine and rizatriptan (18) in single dose pharmacokinetic studies. A review of clinical pharmacology studies and trials of eletriptan, which included patients who received placebo (n=749), eletriptan alone (n=3,908) or eletriptan plus an SSRI (n=253), found no clinically meaningful difference in the incidence of adverse events between the three groups (27). There was no difference in rate of discontinuation of eletriptan because of adverse events and no instance of serotonin syndrome was reported.

Although cases suggestive of serotonin syndrome have been reported when triptans and SSRIs/SNRIs have been used together, when considered in the context of co-prescribing rates, the risk of an interaction appears small. A US study, based on weighted data from a national survey in 2007-2008, estimated that 1.3+ million US patients a year were using the drugs in combination (28). Initial analysis of data from the UK general practice database of combined exposure to an SSRI and a triptan over approximately 5 million patient-years gave insufficient indication of an association with symptoms of serotonin toxicity to justify proceeding with a more detailed study (29).

Additionally, a retrospective population-based database analysis covering a 14 year period assessed the risk of serotonin syndrome with concomitant use of triptans and SSRIs/SNRIs. It identified 19,017(±3) patients who had been co-prescribed a triptan and SSRI/SNRI, 17 of whom were suspected as having developed serotonin syndrome; however, after careful medical record review, the authors identified only two definite cases and five possible cases. The estimated incidence of serotonin syndrome among patients co-prescribed triptans and SSRIs/SNRIs ranged from 0 to 4 cases per 10,000 person-years of exposure; the authors suggested that their data supports the opinion that the 2006 FDA advisory should be reconsidered (30).

Neither European nor UK regulatory authorities have issued a statement subsequent to the FDA alert. However, since 2006 all Summaries of Product Characteristics (SmPCs) for triptans have been updated to include a warning of a possible interaction with SSRIs/SNRIs. Most advise appropriate observation when the combination is given, particularly at the start of treatment, when doses are increased or when another serotonergic medicine is added to the patient's regimen (31-37). The SmPC for over-the-counter sumatriptan does not contraindicate its sale to patients on SSRIs, but states that patients should be advised to talk to their doctor immediately if they experience confusion or uncontrolled muscle movements on the combination (38).

An American Headache Society position paper published in 2010 stated that available evidence does not support limiting use of triptans with SSRIs/SNRIs because of concerns of serotonin syndrome. It encouraged the FDA to revise or rescind their 2006 alert (23). The FDA has since indicated that it is re-evaluating the language used in the alert so that it does not deter combined use of these agents (39); however, as of December 2018, no further comment has been made.

Are there greater risks with individual agents?

Triptans differ considerably in their pharmacokinetic properties (40). Theoretically, triptans with lower lipophilicity, such as frovatriptan and sumatriptan, might be favoured as they are less likely to cross the blood-brain barrier and interact with SSRIs/SNRIs in the central nervous system (CNS). However, in comparative studies of triptans, no clear relationship has emerged between frequency of CNS side-effects and lipophilic properties (40). Again theoretically, it might be rational to avoid, as first-line, the combination of an SSRI/SNRI plus a triptan with a long half-life. Frovatriptan has the longest half-life (26 hours) and sumatriptan, at two hours, the shortest (40). Naratriptan has a potential advantage in that it is excreted mainly unchanged by the kidneys, which makes significant pharmacokinetic interactions unlikely (34).

With regard to current prescribing information, SmPCs for frovatriptan and zolmitriptan specifically note a potential interaction with fluvoxamine, a potent inhibitor of CYP1A2 (33,37). SmPCs for SSRIs, SNRIs and mirtazapine highlight the possibility of an interaction with triptans (6-13,41); only that for citalopram recommends against concurrent use (6) although there is no published evidence to suggest that this agent poses a greater problem in this respect than other SSRIs.

St John's wort

The unlicensed herbal medicine St John's wort (*Hypericum perforatum*), which is used for depression, may increase serotonin levels through weak inhibition of monoamine oxidase and also by inhibiting serotonin re-uptake. In a joint publication, the MHRA and the Swedish Medical Products Agency suggest that, because of the pharmacodynamic interaction between St John's wort and triptans, St John's wort should not be used in patients treated with triptans (42).

Summary

- Using triptans (serotonin agonists) and SSRIs/SNRIs together might be expected to have additive effects on the serotonin system with potential to cause adverse effects.
- In July 2006, the US FDA issued an alert based on a small number of reports of serotonin syndrome during concurrent use of these agents. All UK SmPCs for triptans and SSRIs/SNRIs warn of a possible interaction.
- However, clinical experience indicates that combined use is normally uneventful. If clinically required, a triptan and SSRI/SNRI can be co-prescribed. Current advice is to monitor for signs and symptoms of serotonin syndrome (e.g. restlessness, sweating, tremor, shivering) particularly when treatment is started, when doses are increased, or when another serotonergic medicine is added to the patient's regimen.
- In theory, triptans with lower lipid solubility and a short half-life may be the safer choice (sumatriptan, rizatriptan or zolmitriptan). On the basis of the strength of warnings included in individual SmPCs, prescribers may prefer not to use:
 - fluvoxamine with frovatriptan or zolmitriptan,
 - citalopram with any triptan.
- The MHRA has advised that St John's wort (*Hypericum perforatum*), a herbal medicine used to treat depression, should not be taken with a triptan.

Limitations

The evidence is based on one large retrospective study, case reports and small prospective studies. Only SSRIs/SNRIs licensed for anxiety/depression are considered.

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Search strategy

In-house: Textbooks, resources and databases

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