WHAT ARE THE RISKS ASSOCIATED WITH THE USE OF NSAIDS AS AN ADJUNCT TO SSRIS FOR TREATMENT OF DEPRESSION? AN EVALUATION OF CURRENT EVIDENCE

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SUMMARY

Background: Over the past twenty years, psychiatric researchers have recognised the important role played by inflammation in the pathogenesis of depression. There has been increasing interest in the use of anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), as a way to enhance the efficacy of antidepressant treatments. It is essential that psychiatrists and GPs who prescribe these drugs in conjunction, understand possible interactions, particularly the risk of bleeding.

Subjects and methods: This paper is a literature review regarding NSAID co-prescription with SSRIs and the potential risks and benefits. The objectives of this systematic review are to assess the evidence for the use of NSAIDs as an adjunct to standard antidepressant drugs and evaluate this against the evidence contraindicating such a treatment combination.

Results: Our research suggests that there is evidence to support both the anti-inflammatory benefits of NSAIDs for treating depression, as well as evidence suggesting that NSAIDs increases the risk of bleeding when co-prescribed with SSRIs.

Conclusions: When a broad consideration of the risks and benefits is done, the review is inconclusive about guidelines for co-prescription. More research is required to make strong claims about whether the type of NSAID and duration of treatment influences the risk (or benefit) of co-prescription.

Key words: *depression - antidepressive agents - NSAIDs - SSRIs - bleeding risk*

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Introduction

Clinical depression is experienced by one in four people during their lifetime, and is predicted to be the second most common cause of disability worldwide by 2020 (Andrews, 2008). It is therefore of utmost importance that we seek a safe, effective treatment strategy for clinical depression that brings about good remission rates for patients. Unfortunately, the use of selective serotonin reuptake inhibitors (SSRIs) alone - the current standard treatment for depression - has been shown to bring about remission in less than 50% of patients with clinical depression (Schatzberg, 2008; Trivedi, 2009). It is important for additional treatments to be investigated that might augment the use of SSRIs and bring about recovery and remission in the subgroup of patients who do not respond sufficiently to standard antidepressant treatment.

Over the past twenty years, psychiatric researchers have recognised the important role played by inflammation in the pathogenesis of depression. As a result, there has been increasing interest in the use of anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) as a way to enhance the efficacy of antidepressant treatments (Müller 2006i). Antidepressants are a very commonly prescribed medication, with 11% of women and 6% of men reporting regular use in the UK (Health and Social Care Information Centre, 2013). Therefore, it is crucial that psychiatrists and GPs who prescribe these drugs have a thorough understanding of possible interactions between SSRIs and other commonly prescribed medications. The potential risks and benefits associated with combined use of SSRIs and NSAIDs is an area of particular interest because of what Kohler has referred to as a "bidirectional relationship between depression and pain" (Kohler 2014), whereby patients who are taking antidepressants are more likely to use NSAIDs. Therefore, any adverse risks associated with their combined use requires thorough assessment.

The objectives of this systematic review are to assess the evidence for the use of NSAIDs as an adjunct to standard antidepressant drugs, and evaluate this against the evidence contraindicating such a treatment combination. Objection to co-prescription of SSRIs with NSAIDs centres around a potential increased GI bleeding risk when the two classes of drug are used in combination.

The Immunology Theory of Depression

The evidence base to support an association between inflammation and depression has been growing for the past two decades to establish 'The Immunology Theory' of depression's pathophysiology. It has been suggested that the pathogenesis of depression is at least partly driven by inflammatory processes. The involvement of neural-immune interactions has been proposed as bringing about commonly observed changes in serotonin and adrenaline, both neurotransmitters associated with depression (Müller 1998). In their 2016 review, Kohler et al. suggest that if a depressed patient shows

"specific somatic comorbidities" suggestive of an active inflammatory process, they are more likely to have a better response to combined anti-inflammatory and anti-depressant therapy (Kohler 2016). Monotherapy with an NSAID - such as celecoxib, naproxen or ibuprofen - without an SSRI, had a more significant antidepressant effect than placebo among patients who had active osteoarthritis as well as depression (Iyengar 2013). Patients with depression treated with the COX-2 inhibitor, rofecoxib, for comorbid osteoarthritis noticed an incidental improvement in their depressive symptoms (Collantes-Estevez 2003).

A 2010 meta-analysis confirmed the presence of increased levels of pro-inflammatory cytokines in clinically-depressed patients (Dowlati 2010). Increased levels of inflammatory mediators such as PGE2 and IL-6 (Kronfol 2000, Dowlati 2010, Janssen 2010), TNF-α (Janssen 2010), CRP (Berk 1997) and IL-1 (Howren 2009) have been demonstrated in CSF, serum and saliva from depressed patients without medical comorbidities. Dantzer and Kelley point out that many of the behaviours displayed by patients whose bodies are in an inflammatory state share similarities with those whose behaviour is associated with clinical depression: anhedonia, anorexia and mild cognitive impairment (Dantzer 2007). Administration of inter-feron-α (a pro-inflammatory cytokine) can induce symptoms which are strikingly similar to major depressive disorder, and these in turn respond favourably to standard antidepressant therapies (Raison 2006). Giving pro-inflammatory agents – such as endotoxins and inflammatory cytokines – has been shown to actually induce symptoms of depression in previously healthy subjects (Friebe 2010).

IL-6 is a cytokine of particular interest because its serum concentration has been shown to correlate with severity of depression (Hannestad 2011). Higher serum concentration of IL-6 correlates with more severe depression, and a shift in the individual's circadian rhythm (Alesci 2005).The serum concentration of IL-6 has crucially been shown to decrease in response to SSRI treatment (Basterzi 2005). Therefore, over the past two decades efforts to explore the potential uses of anti-inflammatory drugs as adjuncts to treatment with antidepressants demonstrate that COX2 inhibitors - particularly celecoxib - show promising results (Müller 2006). This effect is due to COX-2 inhibitors' ability to inhibit production of pro-inflammatory mediators such as prostaglandins (PGE2), which is the main product of COX-2 enzyme activity. PGE2 can stimulate the production of IL-6 (Müller 2009) and therefore PGE2 has been suggested as a key component in the pathogenesis of major depressive disorder (Leonard 2001). Further evidence shows that PGE2 concentrations are higher in the CSF of depressed patients, which then lower following antidepressant treatment (Linnoila 1983).

Pharmacological interactions between NSAIDs and SSRIs

The heightened risk of bleeding when SSRIs and NSAIDs are used in combination is acknowledged in the NICE guidance on 'Depression in adults with a chronic physical health problem: recognition and management' [CG91] 2009. The guidelines urge doctors to avoid prescribing NSAIDs in combination with SSRIS: "1.5.2.6 Do not normally offer SSRIs to patients taking non-steroidal anti-inflammatory drugs (NSAIDs) because of the increased risk of gastrointestinal blee-ding." The guidelines go on to suggest that it is prudent to choose an antidepressant "with a lower propensity for, or a different range of, interactions", and lists mianserin, mirtazapine, moclobemide, reboxetine or trazodone as possible alternatives to SSRIs.

There are multiple hypotheses about how exactly NSAIDs and SSRIs interact with each other in vivo to bring about increased GI bleeding risk. Firstly, NSAIDs are metabolised in the liver by cytochrome P450 (CYP) isoenzyme CYP2C9. Any drug which alters the function of this enzyme, would also affect the metabolism of NSAIDs. Some SSRIs have been shown to inhibit CYP2C9, which therefore causes a pharmacokinetic interaction to increase the level of NSAIDS in the blood (Zullino 2005). The degree to which the CYP2C9 iso-enzyme is inhibited depends on the particular SSRI pre-scribed. Fluoxetine and Fluvoxamine are both moderate inhibitors of CYP2C9; Paroxetine, Sertraline and Citalopram do not inhibit the CYP2C9 isoenzyme at all (Spina 2008). Therefore, it should be possible to select SSRIs that are less likely to cause a pharmacokinetic interaction with NSAIDs, and therefore reduce the likelihood of an increased bleeding risk.

Another possible proposed mechanism is that SSRIs induce an increase in gastric acid secretions that may increase the likelihood of ulcers developing, and thus a resultant upper GI bleed. It has been suggested that it may be helpful to prescribe a proton pump inhibitor (PPI), such as omeprazole, alongside SSRIs to reduce this risk (Andrade 2010). Thirdly, both NSAIDS and SSRIs inhibit platelet function but do so via different mechanisms. SSRIs block the ability of platelets to re-uptake serotonin from the circulation, which impairs the ability of platelets to aggregate. This is because the release of serotonin from platelets augments platelet aggregation and therefore it is unsurprising that SSRIs have been shown to impair platelet function (Sere-bruany 2006, Hallbäck 2012, Bismuth-Evenzal 2012).

NSAIDs predominantly exert their effect by inhi-biting COX enzymes, which are responsible for conver-ting PGH2 into thromboxane A2 in platelets. COX enzymes therefore stimulate platelet aggregation, which means that NSAIDs also impair platelet function, prevent aggregation and increase clotting time. The degree to which platelet aggregation is inhibited varies with each specific NSAID, and is related to both dose

and duration of treatment (Kohler 2016). Short-term, sporadic use of ibuprofen at over-the-counter doses shows a low risk of GI bleeds. However, aspirin has a slightly increased risk compared to other NSAIDs as it has a more potent anti-coagulant effect (2008). Since the COX-1 enzyme is involved in thromboxane A2 formation by platelets, it should be the case that using COX-2 selective inhibitors, such as celecoxib, reduces the increased bleeding risk associated with NSAID use.

Evidence for the use of NSAIDs with SSRIs

There is a growing body of evidence that NSAIDs could be an effective adjunct to SSRIs for treating depression. To date, there have been three randomised controlled trials investigating the combined use of SSRIs and NSAID therapy, and all have returned findings in favour of the use of NSAIDs as an adjunctive treatment to SSRIs in depression (Table 1). Each of the three studies chose to investigate celecoxib as their selected NSAID, and the highest dose investigated was 200mg bd. The longest study duration was 8 weeks and the maximum study size was 40 patients, with a combined population size across the three studies of 107 patients. All studies reported no significant increase in risk of GI bleeds nor raised cardiovascular risk factors.

In addition, two population-based case-control studies offer further evidence that combined use of NSAIDs and SSRIs does not cause increased risk of GI bleeds (Tata 2005, Targownik 2009). These two observational studies have much larger population numbers and therefore stronger statistical significance, indicated by the narrow confidence intervals. A population-based cohort study by Dalton et al. analysed 4,165 patient records of individuals who were taking both NSAIDs and SSRIs simultaneously. The study found that the combined use of

NSAIDs and SSRIs corresponded to a rate difference of 16.3cases of GI bleeds per 1000 treatment years (95% CI 7.1–19.5) (Dalton 2003). Therefore, the relatively small group numbers used in the RCT studies in Table 1 (maximum of 40 patients and 8 weeks as longest duration) are unlikely to be sufficiently large to detect the sorts of rate differences seen by Dalton et al. Although the results of the three RCTs are encouraging, they should be treated with caution for this reason.

All three randomised controlled trials found an improvement in depression symptoms and higher remission rates in the combined SSRI and NSAID group compared to SSRI treatment alone. Hashemian et al. argue that "celecoxib adjunctive therapy at the dosage of 200 mg/day may accelerate the onset of therapeutic effect of sertraline". Their research suggests that the rate of improvement of depressive symptoms (measured as an improvement of depressive symptoms from baseline on the Hamilton Depression Score) was significantly faster in the celecoxib group compared to the placebo group over 4 weeks. In addition, the number of patients who achieved remission was five times higher in the celecoxib add-on group. Importantly Hashemian et al. found that the incidence of adverse effects did not differ significantly in either treatment groups: "No major gastrointestinal problems (including bleeding, ulceration and perforation of stomach or intestine) and cardiovascular problems were observed in the patients." Hashemian includes the caveat that "optimal therapeutic effect of sertraline covers up the beneficial effect of celecoxib augmentation within 8 weeks", which suggests that the most important role of celecoxib could be to accelerate the onset of SSRI treatment effects, because SSRIs typically take at least two weeks to improve symptoms. Celecoxib could be considered as a useful adjunct to "speed up the onset" of sertraline's effect (Hashemian 2011).

Table 1. Studies which suggest NSAIDs and SSRIs are safe to be used in combination

Study	Type	Group Size	NSAID	Antidepressant	Adverse Effects?	Treatment Duration
Akhondzadeh et al. 2009 (18)	RCT	n = 37	celecoxib 200 mg bd	Fluoxetine 40mg od	No significant GI bleed risk or cardiovascular risk found.	6 wk
Abbasi et al. 2012 (19)	RCT	n = 40	celecoxib 200 mg bd	Sertraline 200mg od	No significant GI bleed risk found. Cardiovascular not reported.	6 wk
Hashemian et al. 2011 (17)	RCT	n = 30	celecoxib 100mg bd	Sertraline: 25 mg/ day of sertraline for the first 3 days, then 50 mg daily for 4 weeks then increase to 100 mg/day if needed.	No significant GI bleed risk or cardiovascular risk found.	8 wk
Tata et al. 2005 (27)	Population based Case-control	Cases = 11,261 Controls = 53,156	Various NSAIDs	Various SSRIs	Minor increased GI bleeding risk found. OR (95% CI) for GI bleeding SSRI alone: 2.38 (2.08–2.72). NSAIDs alone: 2.15 (2.02–2.28). For combined use vs. control: 2.93 (CI: 2.25–3.82).	not specified
Targownik et al. 2009 (28)	Population based Case-control	Cases = 1552 Controls = 68,590	Various NSAIDs	Various SSRIs	No significant increased bleeding risk found. OR (95% CI) for combined use of NSAID and SSRI vs. NSAID alone: 1.2 (CI: 0.78–1.92).	not specified

Akhondzadeh et al. undertook a randomised controlled trial that lends further "statistically significant support for enhancement of the antidepressant effect of the SSRI fluoxetine by concurrent treatment with celecoxib." The study found that for patients with major depression, celecoxib given in conjunction with an SSRI leads to greater reductions of depression symptoms and higher remission rates when compared to antidepressant use alone (Akhondzadeh 2009). The recommended dose of celecoxib - 400mg/day - was well tolerated, and in the celecoxib group no clinically important side effects were observed. Importantly, no cardiovascular side effects were observed, which was confirmed by normal ECG.

Abbasi et al. found similar evidence to support the use of NSAIDs for treating depression in their randomised double-blind placebo controlled study of 40 patients. The patients in the celecoxib add-on group experienced greater improvement in symptoms (95%) and remission (35%) compared to the placebo group (50% and 5% respectively). Interestingly, they found evidence that the baseline serum IL-6 levels significantly correlated with the baseline Hamilton Depression Scale scores, and the celecoxib group showed greater reduction in serum IL-6 levels than the placebo group. Abbasi et al. concluded that in "supporting previous studies we showed that celecoxib is both safe and effective as an adjunctive antidepressant." (Abbasi 2012).

Tata et al. provided evidence that, when used individually, SSRIs and NSAIDs double the risk of GI bleeds. However, when used together there is no statistically significant increase in bleed risk (NSAID + SSRI: odds ratio [OR] 2.83 (95% CI: 2.39 – 3.34); OR for SSRI use: 2.38 [CI 2.08 - 2.72]; OR for NSAIDs 2.15 (CI 2.02 - 2.28)). Targownik et al. carried out a population based case-control analysis of Canadian patients which found that combined SSRI and NSAID therapy brought about no significant increased bleeding risk (OR (95% CI) for combined use of NSAID and SSRI vs. NSAID alone: 1.2 (CI: 0.78–1.92).The large number of patient records included 1552 patients on combined NSAID and SSRI therapy means that the results have strong statistical significance.

Evidence against the combined use of NSAIDs and SSRIs

As already mentioned, SSRIs have been associated with an increased risk of bleeding, particularly upper GI bleeding, due most probably to inhibition of platelet function and cytochrome P450 isoenzymes. While the bleeding risk associated with SSRIs alone appears low, some studies have found that the risk of GI bleeding substantially increases when SSRIs are combined with NSAIDs (Table 2).

A large population-based case-control study (de Abajo et al. 1999) analysed patient records in the UK General Practice Research Database and found a four-fold increase in the number of patients who had GI bleeds in the group taking both SSRIs and NSAIDs when compared to the patients who were taking only NSAIDs (Table 2). A further cohort study by de Jong et al. found that the incidence rate ratio for the prescription of peptic ulcer drugs was 12 times higher in patients taking concurrent SSRIs and NSAIDs as opposed to an SSRI alone (de Jong 2003). Interestingly, de Jong et al. also found that the group taking concurrent low dose aspirin and SSRI had a lower risk of bleeding (RR 7.2 (95% CI: 3.1 – 17.1) than patients taking other NSAIDs with an SSRI (RR 3.7 (CI: 3.2 to 4.4). This is surprising given that aspirin has been shown to have a higher incidence of GI bleeds compared to other NSAIDs, such as ibuprofen (Moore 1999). The results of these studies (de Abajo 1999, de Jong 2003) show a statistically significant increase in bleeding risk when SSRIs and NSAIDs are used concurrently. However, it is worth noting the wide confidence intervals and therefore potentially high standard error in both sets of results, making these studies less useful for accurately demonstrating the extent to which bleeding risk is increased (Table 2).

Table 2. Studies which suggest NSAIDS and antidepressants are not safe to be used in combination.

Study	Type	Group Size	Adverse Effects
de Abajo et al. 1999 (24)	Population based Case-control	Cases of Upper GI bleeding = 1900, Controls = 10,000	RR (95% CI) of bleeding is 15.6 (CI: 6.6 - 36.6) in patients using SSRIs and NSAIDs compared to controls (non-use). RR (95% CI) for NSAID use alone was 3.7 (3.2 to 4.4).
de Jong et al. 2003 (25)	Population based Cohort	Population given peptic ulcer drug Rx on SSRIs: 1181. Population given peptic ulcer drug Rx on SSRIs and NSAIDs: 86	Incidence rate ratio for Rx of peptic ulcer drugs (95% CI): 12.4 (CI: 3.2 - 48.0) in SSRI + NSAID group vs. 1.2 (Ci: 0.5 - 2.8) in group on SSRI alone.
Dalton et al. 2003 (26)	Population based cohort	Population on SSRIs = 26,005. Population on SSRIs and NSAIDs = 4167	OR (95% CI) of upper GI bleeding episodes was 12.2 (CI: 7.1-19.5) in SSRI + NSAID group compared to 3.6 (CI: 2.7-4.7) on SSRIs alone.
Bak et al. 2002 (29)	Nested Case-Control	Cases using both SSRIs and NSAIDs = 5. Controls = 65	OR (95% CI) for hemorrhagic stroke with both SSRI and NSAID vs. non-users: 2.4 (95% CI: 0.9 - 6.2)

Another large population-based cohort study by Dalton et al., which only studied non-aspirin NSAIDs, found that upper GI bleeds were 3.5 times more prevalent in patients taking concurrent NSAIDs and SSRIs when compared with patients taking SSRIs alone (Dalton 2003) (Table 2). The standard error in this set of results is smaller than in the previous two studies and therefore this study provides a slightly more precise estimate of the actual extent of increased bleeding risk. In addition to GI bleeding risk, one nested case-control study has investigated whether combined use of NSAIDs and SSRIs increases the risk of haemorrhagic stroke (Bak 2002). The results demonstrate an interesting trend towards increased risk of haemorrhagic stroke in patients exposed to both SSRIs and NSAIDs when compared to non-users of either drug (Table 2). However, the results did not reach statistical significance and this line of enquiry requires further investigation.

Discussion

Despite the promising results investigating celecoxib (Hashemian 2011, Akhondzadeh 2009, Abbasi 2012), it is contested whether this evidence is broadly useful and transferable because in the UK, celecoxib is not as widely used as other NSAIDs such as diclofenac, nimesulide and ibuprofen (Arfè 2016). Further efforts should be made to research interactions of SSRIs with common over-the-counter NSAIDs and analgesics such as aspirin, ibuprofen and paracetamol. These are the drugs that are bought and prescribed most frequently alongside antidepressants. Research so far into over-the-counter NSAIDs as an adjunct to SSRIs is limited, but the few studies that do exist show promising results that the combination is effective. One study has shown that monotherapy with ibuprofen led to improvement in depressive symptoms compared to placebo in patients with osteoarthritis and depression (Iyengar 2014). Another pilot study focused on 21 depressed patients who had not responded to SSRI treatment alone. After treatment with 160mg/day of aspirin, 11 out of the 21 patients saw improvements within the first week and sustained this positive response throughout the four weeks of the trial (Mendlewicz 2006). It is worth remembering however, that the risks of common over-the-counter NSAIDs may well be underestimated, as selective COX-2 inhibitors (such as celecoxib) are "considered to have a more targeted anti-inflammatory effect and a decreased risk for gastrointestinal adverse events compared to traditional NSAIDs" (Kohler 2014).

So why do the NICE Guidelines (October 2009) suggest that doctors reconsider the type of antidepressant and not the type of NSAID used in concomitant prescription of SSRIs and NSAIDs? Why does NICE not propose that doctors prescribe a COX-2 inhibitor such as celecoxib as an alternative NSAID in patients taking SSRIs if COX-2 inhibitors are associated with a lower bleeding risk than other NSAIDs, and could provide added benefit to patients with depression?

There is a financial argument here. In a July 2013 report, the cost of celecoxib was roughly ten times that of the cheaper NSAID ibuprofen (Consumer Reports Best Buy drugs , July 2013), but it may be a cheaper intervention overall if the antidepressant effect of the co-therapy is significant. Another reason that celecoxib may not be recommended as a default alternative to other NSAIDs is due to concern about the cardiovascular risk associated with COX-2-selective NSAIDs. In the last 13 years, clinical use of selective COX-2 inhibitors has been cautious in light of this risk. However, studies have indicated it is rofecoxib, and not celecoxib, that causes an increased risk of cardiovascular adverse effects (Solomon 2006i, 2006ii). Even in the case of rofecoxib, it has been suggested that the risk of cardiovascular events depends on the dosage, treatment length and particularly on baseline cardiovascular risk factors of a specific patient (Solomon 2006i). Given this more complicated picture that seems to suggest that celecoxib could both be an advantageous and effective adjunct medication to SSRIs, to what extent is it realistic to suggest prescribing it? These are all questions which merit further investigation.

It is likely that the duration of treatment with NSAIDs could be a significant consideration when analysing the safety of using NSAIDs in conjunction with SSRIs. For example, using NSAIDs for just 4 to 6 weeks at the start of treatment for a depressive episode has been shown to be effective in reducing depressive symptoms in one study (Hashemian 2011). But is this really putting patients at risk of serious bleeding? As discussed earlier, three clinical trials which used celecoxib add-on therapy at doses of up to 200mg bd for 6 to 8 weeks (Hashemian 2011, Akhondzadeh 2009, Abbasi 2012) did not report GI bleeds in their samples, but were limited by small sample sizes. It therefore remains unclear if the use of NSAIDs for a relatively short duration would pose a significant additional bleeding risk to a patient, particularly if they were otherwise healthy with no elevated cardiovascular or bleeding risk factors.

If it is indeed true that the use of NSAIDs alongside SSRIs poses too high a risk of bleeding, perhaps doctors could consider the alternative option of prescribing antidepressants which have been proven to have additional or enhanced anti-inflammatory effects in and of themselves. This could be particularly useful for depressed patients who have raised inflammatory markers and no comorbidities. Kohler 2016 agrees that treatment "algorithms could be improved by selecting antidepressants with anti-inflammatory properties" (Kohler 2016). The example he uses is nortriptyline, a tricyclic antidepressant, which has improved antidepressant effect compared to escitalopram, an SSRI, in patients who have a CRP (C-reactive protein, an inflammatory marker) greater than 3 mg/L (Uher , 2014). Kohler argues that the future of personalised antidepressant treatment may well be tailored in this way to consider inflammatory markers, such as CRP or IL-6, and prescribing drugs which target the inflammatory cascade.

Conclusions and Perspectives

This systematic review has attempted to evaluate all the relevant evidence regarding whether or not there is an increased risk of GI bleeding in combined NSAID and SSRI treatment for depression. Unfortunately, the current review leaves this crucial question unanswered as the evidence remains inconclusive. The randomised controlled trials included in this review are limited by small sample sizes and short study durations. The most useful data comes from observational studies carried out by searching large databases of electronic medical records. These observational studies had very large sample sizes and were better able to detect significant changes in incidence of GI bleeding events than the RCTs (Hashemian 2011, Akhondzadeh 2009, Abbasi 2012). With the RCT's much smaller sample sizes, an increased risk of GI bleeding might not have been detected simply because of the limitations in power. However, the observational studies still suffer from a high degree of standard error in their results, which makes it difficult to draw precise clinical conclusions from the data. Another drawback of the larger observational studies is that they offer no information on which specific types of NSAID or SSRI were given to each patient, so we can only draw general conclusions about SSRIs and NSAIDs as a drug class from these studies.

Additionally, the large observational studies show conflicting findings, with some studies reporting no increased bleeding risk due to combined SSRI and NSAID therapy (Tata 2005, Targownik 2009) and some finding the opposite. As a result, it is not possible to find an answer to our question at this stage, and further research is needed in order to fully clarify whether NSAID SSRI joint therapy causes an increased risk of GI bleeding compared to monotherapy with either type of drug.

Moreover, there are refined considerations to take into account if NSAIDs and SSRIs might one day to be routinely co-prescribed to treat depression. Instead of, or as well as, reconsidering the choice of antidepressant used for treating a patient with depression, clinicians should also consider the type of anti-inflammatory used, for example whether it is COX-2 selective. Another significant factor is the duration of the NSAID treatment, and further research is needed to determine the shortest effective treatment duration so as to limit exposing patients to unnecessarily long courses of NSAIDs when short regimes at the start of SSRI treatment may be equally effective.

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