<table>
<thead>
<tr>
<th>Study</th>
<th>Sources</th>
<th>Summary</th>
<th>Summary (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onder 2004 USA Systematic Clinical Review</td>
<td>Search methodology / Databases searched PubMed/MEDLINE (1965 to 9/2003) PsychINFO Bibliographies of retrieved articles Information from colleagues</td>
<td>Population reports (continued) Psychiatric adverse events for celecoxib and rofecoxib Abnormal dreaming Abnormal thinking Agitation Amnesia Anxiety Confusion Depression Hallucination Insomnia Psychosis Somnolence Psychiatric adverse events for indomethacin Abnormal movements Agitation Anxiety Depersonalization Dizziness Dyspnea Dysphoria Fear Fear of dying Hallucination Panic Psychiatric adverse events (NSAID not specified) Abnormal thinking Amnesia Anxiety Confusion Delirium Depression Emotional lability Hallucination Lethargy Malaise Psychosis Sleep disturbance Case reports N = 41 cases Mean age = 63 (17); 54% aged ≥65 Men and women (34%) Drugs listed in case reports (traditional NSAIDs) Diclofenac Ibuprofen Indomethacin Naproxen Piroxicam Sulindac Tolmetin</td>
<td>Psychiatric adverse events for traditional NSAIDs Diclofenac (n = 3 cases) -depression -hallucination -irritability Ibuprofen (n = 11 cases) -agitation -anxiety -delirium -hallucination IBS (n = 11 cases) -hallucination Ibuprofen (n = 11 cases) -hallucination</td>
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### Summary (continued)

<table>
<thead>
<tr>
<th>Case reports (continued)</th>
<th>Summary (continued)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric adverse events for COX-2s</strong></td>
<td><strong>Who is at risk of NSAID induced psychiatric adverse events (continued)</strong></td>
<td><strong>Population studies</strong></td>
</tr>
<tr>
<td>- celecoxib and/or rofecoxib</td>
<td>Although indomethacin was one of the NSAIDs most commonly responsible for psychiatric adverse events, the reason for this finding remains unclear</td>
<td>Psychiatric events were reported to occur most often within 1 hour of receiving indomethacin with duration of symptoms recorded as &lt;6 hours on average</td>
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<td>- delirium</td>
<td>Of all the available NSAIDs, indomethacin is more frequently associated with CNS adverse events in older patients</td>
<td>The most common events with celecoxib were confusion, somnolence and insomnia</td>
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<td>- hallucination</td>
<td>It is not possible to say whether selective COX-2 inhibitors expose people to a higher risk of psychiatric adverse events than traditional NSAIDs</td>
<td>As a proportion of the total reports hallucination has been reported more commonly with rofecoxib than with celecoxib</td>
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**Potential mechanisms for NSAID-related psychiatric adverse events**

It is not clear how NSAIDs can precipitate the onset of psychiatric symptoms.

There appears a role for prostaglandins in CNS transmission and a possibility that selective COX-2 inhibition may modulate CNS function.

There is evidence of the impact of prostaglandins on catatonic states in animals, noradrenaline release at synapses, modification of postsynaptic effects of transmitter agents and alterations of conduct velocity in isolated nerves.

It has been hypothesized that through the inhibition of prostaglandins, NSAIDs may act as stimulators of dopaminergic transmission.

An additional explanation for the association between NSAID use and psychiatric disturbances may involve the role of fatty acids, which are prostaglandin precursors, in the modulation of the signal transduction mechanisms operating in neuronal membranes and in the synaptic cleft, and their interaction with various neurotransmitters including serotonin, catecholamines and acetylcholine.

Depression, affective disorders, ADHD, psychological stress and schizophrenia have been related to fatty acid metabolism.

**Who is at risk of NSAID induced psychiatric adverse events**

Studies report conflicting findings regarding age/gender predisposition to adverse psychiatric effects of NSAIDS.

Individuals with pre-existing psychiatric disorders appear to have a higher risk of experiencing adverse psychiatric events associated with NSAID use.

Patients with a history of psychiatric disease may already have dysregulation of neurotransmission, which in some cases is directly mediated by prostaglandins.

In many cases the onset of the reaction to COX-2s has occurred within 24 hours of the first dose.

Population study data relies on voluntary reporting systems and therefore may not reflect the total number of events nor the incidence in terms of total patients exposed to the drug during the study period.

**Case reports**

Depression (n = 15), psychosis (n = 9) and paranoia (n = 7) were the most frequently observed symptoms.

Pre-existing psychiatric illness was documented in 16 (39%) of the cases.

In 6 cases more than one NSAID was used in the same patient.

In all but 1 case, NSAIDs were prescribed at recommended/therapeutic doses.

In general, the adverse event was reported to occur within 24 hours of NSAID consumption and in most cases psychiatric symptoms ceased after discontinuation of the NSAID.

**General comments**

To date, reports of NSAID-related psychiatric adverse events have mostly commonly involved indomethacin and selective COX-2 inhibitors.

Whether this reflects a greater incidence of such events with these drugs or is related to other factors such as usage and reporting patterns is unknown.

Prescribers should consider warning patients of the possibility of an acute neuropsychiatric event when traditional NSAIDs or selective COX-2 inhibitors are prescribed.

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**Conclusion:**

Psychiatric symptoms are a rare but relevant complication of NSAID use. This effect is probably a consequence of impairment in the neurotransmission modulated by prostaglandins when NSAIDs are used by susceptible individuals. This drugs should be used with caution in high risk individuals with pre-existing psychiatric illness.