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NSAID-Related Psychiatric Adverse Events

Who is at Risk?

Graziano Onder,[1,2] *Francesca Pellicciotti*,[1] *Giovanni Gambassi*[1,3] and *Roberto Bernabei*[1]

1 Centro Medicina dell'Invecchiamento, Università Cattolica del Sacro Cuore, Rome, Italy
2 Section of Gerontology and Geriatrics, Sticht Center on Aging, Wake Forest University – School of Medicine, Winston Salem, North Carolina, USA
3 Center for Gerontology and Health Care Research, Brown University – School of Medicine, Providence, Rhode Island, USA

Abstract

NSAIDs are frequently used in clinical practice and they account for approximately 5–10% of all drug prescriptions. NSAID use has been associated with a risk of adverse events, which have a relevant impact on morbidity and mortality and account for a substantial increment of healthcare costs. Less common, but clinically relevant, adverse events associated with NSAID use are the impairment of the CNS and, particularly, the appearance of psychiatric symptoms. These symptoms include changes in cognition, mood state and even precipitation or exacerbation of pre-existing psychiatric disorders. This article aims to review the medical literature on published reports of NSAID-related psychiatric adverse events, identify risk factors for these events and describe mechanisms potentially involved in their onset.

We identified 27 reports with data on 453 cases of NSAID-related psychiatric adverse events. Data suggest that individuals who may be particularly susceptible to such events include patients with a history of psychiatric illness and possibly parturients. Indometacin and selective cyclo-oxygenase (COX)-2 inhibitors were the most frequently reported culprit drugs; however, whether this reflects an increased incidence with these drugs compared with other NSAIDs or factors such as usage or reporting patterns is unknown.

A possible explanation for the psychiatric effect of NSAIDs resides in the modulation of central neurotransmission by prostaglandins, the synthesis of which is inhibited by NSAIDs. COX-2 is a key enzyme in this process since its activity is localised in distal dendrites and dendritic spines, which are cellular specialisations involved in synaptic signalling. Dopamine is considered the most relevant neurotransmitter involved in this phenomenon.

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

reports of NSAID-related psychiatric adverse events have most commonly involved indometacin and selective COX-2 inhibitors. Prescribers should consider warning patients of the possibility of an acute neuropsychiatric event when traditional NSAIDs or selective COX-2 inhibitors are prescribed.

NSAIDs are a very commonly prescribed group of medications, accounting for approximately 5–10% of all prescriptions in Western countries.[1] More than 100 million prescriptions for NSAIDs are written annually in the US, and several of these drugs are available in many countries as over-the-counter preparations.[2] NSAIDs have a wide spectrum of anti-inflammatory, analgesic, antipyretic and platelet inhibitory actions. The most common indications for their use are rheumatic diseases, degenerative joint diseases, and acute or chronic pain syndromes.[3] In addition, it has recently been proposed that NSAIDs may slow or prevent the onset of Alzheimer's disease by treating the putative inflammatory process of this illness. These drugs have also been suggested to reduce the inflammatory component of cystic fibrosis and protect against the onset of gastrointestinal cancers.[4-6]

The use of NSAIDs has been associated with an elevated risk of adverse events, which are commonly responsible for hospital admissions, have a relevant impact on morbidity and mortality, and account for a substantial increase in healthcare costs.[7-9] About 21% of all the adverse events reported to the US FDA and 25% of events reported to the UK Committee on Safety of Medicines are associated with NSAID use.[10] Gastrointestinal adverse events are the most prevalent, but renal, hepatic and cardiovascular complications can also be observed with the use of these drugs.[11-14]

Less common but clinically relevant adverse effects associated with NSAID use include impairment of the CNS and, particularly, occurrence of neuropsychiatric symptoms.[15,16] These neuropsychiatric symptoms include changes in cognition, mood and even precipitation or exacerbation of pre-existing psychiatric conditions. Several cases of NSAID-associated neuropsychiatric symptoms have been reported in the medical literature in the past decades,[15,16] but this subject has rarely been evaluated systematically and no predisposing factors have been identified for these adverse events.

After a carefully conducted and extensive literature search, the aims of this review were to: (i) list and describe the published studies reporting cases of NSAID-related psychiatric adverse events; (ii) describe mechanisms potentially involved in their onset; and (iii) identify risk factors for these events.

1. Review of Published Studies on NSAID-Related Psychiatric Adverse Events

1.1 Search Strategy

Studies reporting cases of NSAID-related psychiatric adverse events were identified through PubMed searches of the Medline database using the following terms: 'adverse event' and 'non-steroidal anti-inflammatory drugs', matched, in separated searches, with each of the following terms: 'anxiety', 'depression', 'psychosis', 'hallucinations' and 'cognition'. The search included the period between 1965 and September 2003. An additional search using the PsychINFO database was performed. Non-English language articles were not included in the search. In addition to case reports, letters to the editor, commentaries, review articles, editorials and observational studies were also included. Bibliographies of the retrieved articles were searched to identify other eligible studies and information from colleagues was used to identify more recently published articles.

All NSAIDs, including the selective cyclo-oxygenase (COX)-2 inhibitors, were included.

Table I. Population studies reporting psychiatric adverse events induced by NSAIDs. Studies are listed by year of publication

Source (year of publication)	No. of cases	Age (y)	Drug(s)[a]	Adverse event(s)[a]
New Zealand Medicines Adverse Reactions Committee[16] (1992)	150	<30y: 15 cases; 30–59y: 83 cases; ≥60y: 52 cases	NR	Confusion (29), depression (20), hallucination (19), lethargy (19), sleep disturbance (17), malaise (14), anxiety (7), amnesia (6), emotional liability (6), abnormal thinking (6), psychosis (4), delirium (3)
Canadian Adverse Drug Reaction Monitoring Program[18] (2000)	26	NR	Celecoxib (26)[b]	NR
New Zealand Intensive Medicines Monitoring Programme[19] (2002)	13	NR	Celecoxib (11), rofecoxib (2)[b]	Confusion (5), hallucination (3), depression (2), psychosis (1), anxiety (1), abnormal thinking (1)
Australian Adverse Drug Reactions Advisory Committee[20] (2003)	191	NR	Celecoxib (142), rofecoxib (49)[b]	Confusion (39), somnolence (28), insomnia (27), hallucination (23), depression (21), abnormal thinking (19), agitation (17), abnormal dreaming (13), amnesia (11)
Saskatchewan Adverse Drug Reaction Reporting Program[17] (2003)	32	31 (average)	Indometacin (32)[c]	Dizziness (23), agitation (12), anxiety (12), fear (9), dyspnoea (8), dysphoria (7), depersonalisation (4), panic (4), fear of dying (4), hallucination (4), abnormal movements (2)

a The number of cases is reported in brackets; some patients experienced more than one symptom.

b Studies reported data on celecoxib only[18] or rofecoxib and celecoxib.[19,20]

c Study reported data on indometacin only.

NR = not reported.

1.2 Findings

The search strategy led to the identification of 27 relevant reports: 5 population[16-20] and 22 case reports.[15,21-41] Overall, 453 cases of NSAID-related psychiatric events were reported in these studies. Table I and table II present the characteristics of cases described in the population and case report studies, respectively.

1.2.1 Population Studies

Using a national database, Clark and Ghose[16] described prevalence of adverse drug events associated with NSAID use spontaneously reported to the New Zealand Medicine Adverse Reactions Committee between 1970 and 1989. Over the 20-year period examined in the study, 150 psychiatric adverse events associated with NSAIDs were reported, including (listed from most to least common): confusion (29 cases); depression (20); hallucination (19); lethargy (19); sleep disturbance (17); and malaise (14). Other less common events were anxiety, amnesia, emotional liability, abnormal thinking, psychosis and delirium (table I). Nearly two-thirds of the reactions were reported among women. In this study, the number of psychiatric reactions rose with advancing age until 60 years, and then declined in older individuals. A temporal pattern was also evident, with psychiatric events being increasingly reported between 1974 and 1984, followed by a decline after 1984. The authors suggested that this trend highlights a marked increase in NSAID use over that time period, and the availability of NSAIDs with a better safety profile after 1984. Data on the psychiatric history of the affected individuals and on the specific ingredient responsible for the adverse events were not available.

In a more recent study, Clunie et al.[17] reviewed the records of patients experiencing postpartum complications in a university hospital in Canada between 1994 and 1999 to identify adverse drug reactions attributed to indometacin. Additional cases of indometacin-induced adverse effects were

Table II. Case reports describing psychiatric adverse events induced by NSAIDs. Studies are listed by year of publication

Study (year of publication)	No. of cases	Age (y)	Drug(s)[a]	Adverse event(s)[a]	Psychiatric history[a]
Boyle[21] (1965)	2	NR	Indometacin (2)	Psychosis (2)	No (2)
Rothermich[22] (1966)	1	73	Indometacin	Depersonalisation	No
Thompson and Percy[23] (1966)	5	NR in 4 patients	Indometacin (4)	Depression (4)	No (5)
		72	Indometacin	Hallucination	
Carney[24] (1977)	1	65	Indometacin	Psychosis	No
Gotz[25] (1978)	1	80	Indometacin	Psychosis	No
Kruis and Barger[26] (1980)	1	53	Sulindac	Psychosis	No
Thornton[27] (1980)	1	53	Sulindac	Delirium	Yes
Goodwin and Regan[28] (1982)	8	Range: 67–82	Naproxen (4), ibuprofen (4)	Forgetfulness (4), inability to concentrate (3), depression (3), paranoia (2), irritability (1), disorientation (1)	No (8)
Griffith et al.[29] (1982)	1	37	Ibuprofen	Psychosis	Yes
Schwartz and Moura[30] (1983)	1	61	Indometacin	Depersonalisation, anxiety	No
Sotsky and Tossell[31] (1984)	1	56	Tolmetin	Mania	No
Browning[32] (1996)	4	Range: 42–67	Naproxen (4), diclofenac (2), ibuprofen (1)	Depression (4), paranoia (3), hypomania (1)	Yes (4)
Mallet and Kuyumjian[33] (1998)	1	92	Indometacin	Agitation	Yes
Jiang and Chang[15] (1999)	5	Range: 37–57	Naproxen (3), ibuprofen (2), sulindac (1), diclofenac (1), piroxicam (1)	Depression (4), paranoia (1), hypomania (1)	Yes (5)
Ritter and Eskin[34] (1998)	1	16	Ibuprofen	Agitation	Yes
Nassif and Ritter[35] (1999)	1	58	Indometacin	Psychosis	No
Tharumaratnam et al.[36] (2000)	1	88	Indometacin	Psychosis, paranoia	No
Lantz and Giambanco[37] (2000)	1	78	Celecoxib	Hallucination	Yes
Macknight and Rojas-Fernandez[38] (2001)	1	81	Celecoxib, rofecoxib	Delirium	No
Katz et al.[39] (2002)	1	27	Ibuprofen	Psychosis	Yes
Bernstein and Werlin[40] (2003)	1	76	Ibuprofen	Pseudodementia	No
Eser et al.[41] (2003)	1	72	Piroxicam	Hallucination, anxiety	Yes

a The number of cases is reported in brackets; some patients experienced more than one symptom or received more than one NSAID.

NR = not reported.

identified from the Saskatchewan Adverse Drug Reaction Reporting Program. The authors identified psychiatric events related to indometacin use in 32 parturients (mean age 31 years). Dizziness (23 cases) was the most commonly observed symptom, followed by agitation (12) and anxiety (12). Events reported by fewer than ten patients included fear, dyspnoea, dysphoria, depersonalisation, panic, fear of dying, hallucinations and abnormal movements (table I). Psychiatric history was not documented in any case. Noticeably, psychiatric events were reported to occur most often within 1 hour of receiving indometacin, with duration of symptoms recorded in 24 cases as being, on average, <6 hours.

In recent years, several national reports described psychiatric adverse events associated with use of the newer selective COX-2 inhibitors. In 1999, 26 cases of psychiatric adverse drug events related to celecoxib were reported to the Canadian Adverse Drug Reaction Monitoring Program.[18] In New Zealand in 2002, the Intensive Medicines Monitoring Pro-

gramme received 13 reports of cases of acute psychiatric events related to COX-2 inhibitor use (celecoxib, 11 cases; rofecoxib, 2 cases).[19] Five of the reports were of confusion, two of depression and three of hallucination. Exacerbation of manic depressive psychosis was also reported in one case. Anxiety and abnormal thinking were reported once. In this report, most of the patients were elderly, there were more reports involving women than men and the psychiatric events rapidly resolved upon withdrawal of the COX-2 inhibitor in each case. Finally, in 2003 the Australian Adverse Drug Reactions Advisory Committee reported 142 (5% of the total number of adverse drug reactions reported for the drug) cases of acute neuropsychiatric events associated with celecoxib and 49 (8%) with rofecoxib.[20] These numbers were calculated after exclusion of psychiatric events that might have been associated with other events such as a hypersensitivity reaction or hyponatraemia. The most common events with celecoxib were confusion, somnolence and insomnia. As a proportion of the total reports, hallucination has been reported more commonly with rofecoxib than with celecoxib. In many cases the onset of the reaction was dramatic: the event occurred within 24 hours of the first dose in 36 cases with celecoxib and in 14 cases with rofecoxib. In 12 and 4 cases, respectively, the reaction recurred with re-exposure to the drug.

In interpreting these population study data, some limitations should be considered. The data are largely based on voluntary reporting systems and may not reflect the total number of such events that have occurred. Furthermore, as the data represent the number of events reported rather than the incidence in terms of the total number of patients exposed to the drug over the studied time period, it is not possible to determine whether the events occurred more commonly with one drug than another.

1.2.2 Case Report Studies

In addition to the five population studies, 22 case report studies described 41 cases of NSAID-related psychiatric adverse events (table II).[15,21-41] Mean age ± standard deviation of patients included in these studies was 63 ± 17 years; 19 (54%) were ≥65 years and men were represented more than women (21 men, 14 women). However, in six cases age and sex were not reported. Depression (15 cases), psychosis (9) and paranoia (7) were the most frequently observed symptoms and pre-existing psychiatric illness was documented in 16 cases (39%). In these case report studies indometacin was the most frequent culprit drug (14 cases), followed by naproxen (11), ibuprofen (11), diclofenac (3) and sulindac (3); however, these numbers may not reflect the comparative incidences that would be seen if the event rates were adjusted for usage rates of each drug. Two cases related to the use of COX-2-specific inhibitors were described.[37,38] In six cases, more than one NSAID was used in the same patient.[15,32,38]

In one case the onset of neuropsychiatric symptoms was related to an overdose,[34] while in all other cases NSAIDs were used at a therapeutic dosage. Generally, the adverse event was reported to occur within 24 hours of NSAID consumption, and in most cases psychiatric symptoms ceased after discontinuation of NSAID, and re-use of or re-challenge with the same or a different type of NSAID resulted in the recurrence of the symptoms.

2. Potential Mechanisms for NSAID-Related Psychiatric Adverse Events

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

NSAIDs block the synthesis of prostaglandins by inhibiting the activity of COX. This enzyme has shown to have a key role in the CNS, particularly in thermoregulation and pain. COX-2 is the most abundant COX isoform found in the CNS, and it has been identified in neocortex, hippocampus, amygdala, limbic cortices and in nuclei adjacent to the third ventricle, both in neurones and in the non-neuronal cells.[42] COX-2 is upregulated by normal or by abnormal (convulsive) nerve activity, and it is preferentially localised in distal dendrites and dendritic spines, which are cellular specialisations involved in synaptic signalling.[43] These findings suggest a role for prostaglandins in CNS transmission and raise the

possibility that selective COX-2 inhibition may modulate CNS function.

More than 20 years ago, Horrobin[44] and Horrobin and Manku[45] described a potential role for prostaglandins in depression, mania and schizophrenia. They offered evidence related to the impact of prostaglandins on catatonic states in animals, noradrenaline (norepinephrine) release at synapses, modification of postsynaptic effects of transmitter agents and alterations of conduct velocity in isolated nerves. Thus, it is conceivable that central neurotransmission may be altered when the modulation by prostaglandins is lost, especially in susceptible individuals.

Dopamine is probably the most relevant neurotransmitter involved in this phenomenon. Indeed, the dopamine system is involved in psychosis associated with both schizophrenia, a disorder thought to be related to hyper-dopaminergic activity, and long-term amphetamine use, a drug causing dopamine release.[46,47] It has been hypothesised that, through inhibition of prostaglandins, NSAIDs may act as stimulators of dopaminergic transmission.[48] Van Kammen et al.[49] showed that, among patients with schizophrenia, reduction in prostaglandin (PG) E1 levels can cause an increase in dopamine levels. Furthermore, Kaiya et al.[50] found that three of six patients with schizophrenia responded to intravenous injections of PGE1 (alprostadil). Vaddadi[51] showed that patients with schizophrenia who received dihomogammalinoleic acid, a precursor of PGE1, demonstrated a significant decline in both hallucinations and concept disorganisation. Finally, Kanof et al.[52] showed a subsensitivity of platelets to prostaglandins in patients with schizophrenia. If this finding extends to the brain receptors of prostaglandins, then patients with schizophrenia may lack the prostaglandin-mediated 'braking mechanism' that limits the activity of dopaminergic systems, leading to an excess of dopamine in the brain.

Review of this evidence suggests that inhibition of prostaglandins by NSAIDs can increase dopamine levels. It can be hypothesised that these increased levels of dopamine may have a central role in the onset of adverse psychiatric events. In addition, an increased sensitivity to dopamine may explain the high frequency of NSAID-related psychiatric adverse events observed in parturients.[17,53,54] Indeed, in animal models it has been proven that estrogens may exert several effects on the nigrostriatal dopamine system. The first effect is a rapid decrease in dopamine function. The second effect, which develops more slowly and may require higher doses, involves an increase in the density of dopamine receptors. Therefore, estrogens have an early functional dopamine block effect, which is followed by an increment in number of dopamine receptors or dopamine system supersensitivity. The postpartum period, characterised by a fall in estrogen levels, might then represent a period of sudden unmasking of an increased number of dopamine receptor sites in the brain.[53] In this context, an increased dopaminergic transmission induced by NSAIDs may result in an overstimulation of the dopaminergic system, particularly in the mesolimbic system and in the caudatum and putamen, and then result in the rapid onset of psychosis and movement disturbances.

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.[55] In particular, depression, affective disorders, attention-deficit hyperactivity disorder, psychological stress and schizophrenia have been related to fatty acid metabolism.[55]

Another hypothesis considers the similarity of the indolic moiety of indometacin and sulindac to that of serotonin as a possible causative factor in the development of psychosis.[56] However, this hypothesis is unlikely because other NSAIDs with a different molecular structure may also cause psychiatric adverse events.

Finally, there is evidence of decreased cerebral blood flow with indometacin, which coincides with

its peak levels and, hence, may contribute to CNS effects.[57]

3. Who is at Risk of NSAID-Induced Psychiatric Adverse Events?

The identification of predisposing factors for the onset of NSAID-related psychiatric adverse events is difficult because of the paucity of cases reported in the medical literature.

On a theoretical basis, one could have hypothesised that patients using NSAIDs more frequently, namely women and older adults, would have been exposed to a higher risk of presenting such an adverse effect.[2] However, Clark and Ghose[16] identified the highest risk of NSAID-related psychiatric adverse effects in middle-aged patients (age 30–60 years), while a reduced risk was observed in advanced age. This result contrasts with the progressively increased risk of NSAID-related gastrointestinal and haematological adverse events associated with advancing age, with individuals ≥60 years being more susceptible. However, the finding by Clark and Ghose[16] could simply indicate an under-reporting of psychiatric adverse events among older adults, in whom such symptoms may be attributed to CNS diseases associated with the aging process rather than to an adverse event related to the use of a medication.[58]

Overall, based on the results of the studies presented in this review, it seems plausible to state that individuals with pre-existing psychiatric disorders and possibly parturients have a higher risk of experiencing adverse psychiatric events associated with NSAID use. This circumstance suggests the presence of a lower threshold for the adverse effect of NSAIDs in these individuals. As mentioned in section 2, parturients may have a supersensitivity of the dopamine system, as a consequence of the increment in the number of dopamine receptors induced by estrogens, and, therefore, they may be more susceptible to the dopaminergic effect of NSAIDs.[17,53]

Similarly, patients with a history of psychiatric disease may already have dysregulation of neurotransmission, which in some cases, as in patients with schizophrenia, is directly mediated by prostaglandins (see section 2). Therefore, in such a susceptible population, the use of NSAIDs may result in a precipitation of psychiatric illness.

After reviewing all cases, indometacin was one of the NSAIDs most commonly responsible for psychiatric adverse events. The reason for this finding remains unclear. The similarity of the molecular structure of indometacin with that of serotonin has been proposed as a possible causative factor in the development of psychosis.[56] Indeed, the use of indometacin is considered inappropriate in older adults on the basis of Beers' criteria[59] because, of all the available NSAIDs, it is more frequently associated with CNS adverse events.[59,60] However, data on indometacin have been largely based on voluntary reporting systems, which did not consider usage patterns. Therefore, it is not possible to determine for certain if this drug is more frequently associated with psychiatric adverse eventts than other NSAIDs. Newer and safer NSAIDs are now available on the market and their use is the most likely explanation for the reduction in the incidence of NSAID-related adverse events in recent years, as documented by Clark and Ghose.[16]

In contrast with this latter finding, a number of cases have been reported in which the new selective COX-2 inhibitors were responsible for psychiatric events. Indeed, the demonstration of COX-2 activity in patchy arrangements in dendritic branches and spines suggests that COX-2 is not diffusely distributed in the brain, but is targeted and, most likely, associated with specific membrane compartments (section 2). This particular localisation supports the hypothesis that COX-2 has a key role in modulation of neurotransmitter release and inhibition of this enzyme can induce psychiatric symptoms in susceptible individuals.

It is hard to say whether selective COX-2 inhibitors do expose individuals to a higher risk of psychiatric adverse events than traditional NSAIDs. On a theoretical basis, traditional NSAIDs, administered at a therapeutic dosage, produce an inhibition of COX-2 as strong as selective COX-2 inhibitors.[61] In addition, we cannot exclude the fact that the

apparently higher number of psychiatric adverse events reported for selective COX-2 inhibitors may be related to the fact that these drugs have been investigated in larger studies, and more accurately, than traditional NSAIDs.

Among selective COX-2 inhibitors, celecoxib was more often responsible for psychiatric adverse events than rofecoxib. As pointed out in several reports, this finding may reflect a different pattern of use of these drugs.[18-20] Finally, further questions regarding the role of selective COX-2 inhibitors in the onset of psychiatric symptoms are raised by a recent study showing a beneficial antipsychotic effect of these drugs when used in association with antipsychotics to treat patients with schizophrenia.[62]

4. Conclusions

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. These drugs should be used with caution in high-risk individuals with pre-existing psychiatric illness and caution may also be advisable in the postpartum period. To date, reports of NSAID-related psychiatric adverse events have most commonly involved indometacin 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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Correspondence and offprints: Dr *Graziano Onder*, Centro Medicina dell'Invecchiamento, Università Cattolica del Sacro Cuore, Policlinico A. Gemelli, L.go Francesco Vito 1, 00168 Roma, Italy.
E-mail: graziano_onder@rm.unicatt.it