

Psychosis after buprenorphine, heroin, methadone, morphine, oxycodone, and tramadol withdrawal: a systematic review

M.T. LOZANO-LÓPEZ^{1,2}, S. GAMONAL-LIMCAOCO^{1,2}, N. CASADO-ESPADA^{1,2,3}, L. AGUILAR^{1,2,3}, B. VICENTE-HERNÁNDEZ¹, L. GRAU-LÓPEZ⁴, A. ÁLVAREZ-NAVARES^{1,3}, C. RONCERO^{1,2,3}

¹University of Salamanca Healthcare Complex, Psychiatry, Salamanca, Spain

²University of Salamanca, Institute of Biomedicine of Salamanca, Salamanca, Spain

³Psychiatric Unit, School of Medicine, University of Salamanca, Salamanca, Spain

⁴Addictions and Dual Diagnosis Section. Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, CIBERSAM, Spain

Abstract. – OBJECTIVE: This study's main objective is to carry out a systematic review of the onset of psychotic symptoms after opioid withdrawal. The opiate dependence correlated to psychiatric symptoms has been well described.

MATERIALS AND METHODS: Following the PRISMA methodology. The consecutive search strategy was applied: (morphine OR buprenorphine OR oxycodone OR tramadol OR fentanyl OR remifentanyl OR opioids OR heroin OR methadone) AND (Psychosis OR psychotic symptoms OR schizophrenia).

RESULTS: 12 case reports, 3 series of cases, 2 clinical studies, and 2 reviews were found. It seems that the time association is present in all of them; symptoms appear days after the interruption of the opioid. Most of the articles reported are case reports that describe symptoms that appear after the suspension of the opioid substance; in most cases, the reintroduction of the opioid had therapeutic effects and provoked a remission of these symptoms. These preliminary findings indicate that opiates could have an antipsychotic effect; however, the literature is scarce. It is critical to consider, if needed, in opioid-dependent patients who start with psychosis after the opioid withdrawal the possible replacement or reintroduction of opioids to prevent further deterioration in the patient's mental status.

CONCLUSIONS: This study encompasses a comprehensive description of the literature concerning the possible not well-studied outcome of opioid withdrawal. There are some reports of temporal association between withdrawal and psychotic symptoms that improved after the reintroduction of the opioid; it could be taken into consideration in the clinical practice.

Key Words:

Psychosis, Schizophrenia, Opioids, Withdrawal.

Introduction

The relation between opioid dependence and the existence of mental disorders has been thoroughly described^{1,2}. Studies throughout the years debate about the possible relation between intoxication or dependence of substance use and the onset of psychosis³. A dose-response relationship between the experience of psychotic symptoms and drug dependence has been proposed⁴, especially in adolescents and young adults⁵. Nonetheless, the relevance and influence of opioids on the presence of psychotic symptoms has not been studied systematically, and it seems that there are opposite effects to the other drugs^{6,7}. There are data, mainly case reports or observational studies, that associate the onset of psychotic symptoms due to opioid withdrawal. There are case series showing hypomanic symptoms after opioid withdrawal^{8,9} or psychotic symptoms after opioid withdrawal, such as heroin¹⁰, tramadol, or oxycodone withdrawal¹¹⁻¹³. Additionally, psychotic symptoms have been described after using drugs to treat opioid withdrawal, such as a maintenance program of methadone¹⁴⁻¹⁷, buprenorphine⁸⁻²⁰, or unspecified opioids²¹. On the other hand, opioids, specifically methadone, have been suggested as a potential antipsychotic drug^{22,23}, and case reports show the use of this treatment, even as the only treatment for schizophrenia^{7,24}. Also, Schmauss

et al²⁵ suggest buprenorphine as an antipsychotic treatment. Although the intensity, time, and form of the symptomatology remain unclear, the reports on methadone withdrawal help understand the withdrawal's possible consequences. Cobo et al¹⁴ explain how methadone withdrawal usually resembles the classic symptoms of psychosis up to 36h after the last use of methadone. However, this is a debatable topic in which there is no standard view about opioids and psychotic symptoms, nor studies that describe or study the factors associated with the onset of these symptoms. This study's main objective is to carry out a systematic review of the onset of psychotic symptoms after opioid withdrawal.

Materials and Methods

Search Strategy

Following the PRISMA methodology²⁶, a systematic literature review was performed, searching in the PubMed database to obtain 18 articles published in all languages and 1 article added via references. All articles regarding the presentation of psychotic symptoms with opioid/opiate withdrawal published until May 2019 were included. The following keywords were used: *Morphine*, *Buprenorphine*, *Oxycodone*, *Tramadol*, *Fentanyl*, *Remifentanyl*, *Methadone*, *Heroin*, *Opioids*, *Withdrawal*, *Psychosis*, *Psychotic Symptoms* and *Schizophrenia*. The consecutive search strategy was applied: (morphine OR buprenorphine OR oxycodone OR tramadol OR fentanyl OR remifentanyl OR opioids OR heroin OR methadone) AND (Psychosis OR psychotic symptoms OR schizophrenia) as subject word and random word for all fields. Two members independently selected data from eligible articles and screened the following fields: first author, year of publication, kind of substance, symptoms displayed, and most relevant characteristics of each article. Articles in English, Spanish and Russian were revised. The disagreements were settled through discussion or, if required, consulted to a third member of the reviewing team.

Selection Criteria

The articles included showed psychosis, psychotic symptoms, or schizophrenia triggered by opioid withdrawal. The primary outcome had all kinds of opioid interactions with psychosis, so the selection was filtered with the opioid name plus "withdrawal". Articles about fentanyl and

remifentanyl were not found. The secondary outcome was closer to the topic sought. All articles that were not about humans were discarded (Figure 1).

Results

Tramadol and Oxycodone

We describe the evidence of psychotic symptoms due to the withdrawal of tramadol^{12,13} and oxycodone¹¹ (Table I). Regarding tramadol, we found 2 articles. Senay et al¹³ described that one out of 8 tramadol withdrawal cases showed a mixture of typical opioid withdrawal symptoms with unusual features such as intense anxiety, depersonalization, delusions, confusion, hallucinations, and other symptoms. No correlation between age, sex, and duration with atypical symptoms was reported, but a probable relationship between more tramadol doses per day with

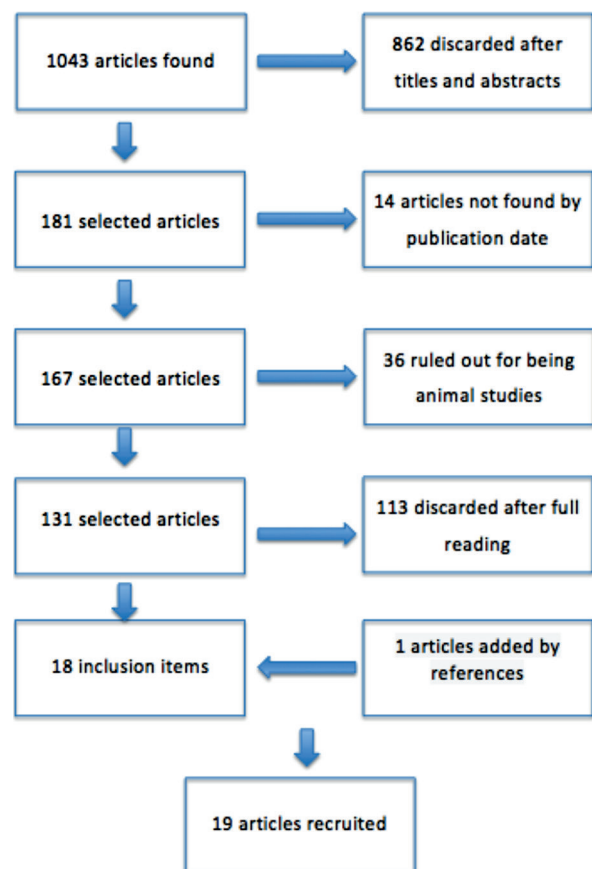


Figure 1. Flowchart of selection of studies for inclusion in umbrella review (PRISMA 2009 flow diagram)¹⁹.

Table I. Psychotic symptoms following oxycodone and tramadol withdrawal.

Authors	Year	N	Drug	Withdrawal symptoms	Evolution
Casado-Espada et al ¹¹	2019	1	Oxycodone withdrawal	The patient started to show persecutory delusions of being harmed and drugged, with possible olfactory and kinesthetic hallucinations, delusions of reference and a tendency towards social isolation	Withdrawal of 10 mg oxycodone/day produces psychotic symptoms in the patient; however, the fact that the patient responded well to the antipsychotics and did not need opioid reintroduction in order for the symptoms to stop does not allow us to establish an unequivocal cause-effect relationship between the symptoms and the withdrawal from the drug.
Rajabizadeh et al ¹²	2009	1	Tramadol withdrawal	Persecutory delusion, delusional mood, first stage of trema, Lilliputian hallucinations.	He was taking 300 mg of tramadol per day until a week ago when he suddenly stopped taking tramadol and he began to have these symptoms
Senay et al ¹³	2003	422	Tramadol withdrawal	1 in 8 tramadol withdrawal cases presented as a mixture of classical opioid withdrawal with other atypical symptoms.	These data would suggest that a relatively small number of patients (55 out of 422 patients) are susceptible to the atypical withdrawal symptoms that were observed.

a higher risk of atypical symptoms was noted¹³. Rajabizadeh et al¹² described a clinical case of psychotic symptoms due to a sudden atypical tramadol withdrawal syndrome when the patient stopped consuming tramadol. The patient said that he was fearful because security police had been following and threatening him. He also believed that some black points were formed in his memory, and he could see God on television and see some tiny creatures around him. He had other withdrawal symptoms like diarrhea, tremors, rhinorrhea. All these symptoms disappeared with analgesics, sedatives, and hypnotic drugs, but not with antipsychotics¹². Regarding oxycodone, Casado-Espada et al¹¹ described a case of a 36-year-old male patient without personal or familiar psychiatric records who took this drug due to chronic rachialgia and presented psychotic symptoms (persecutory delusions, with possible olfactory and kinesthetic hallucinations) after oxycodone withdrawal. These symptoms disappeared with antipsychotic drugs¹¹.

Buprenorphine, Methadone, and Morphine

Below, we describe the evidence of psychotic symptoms following withdrawal from buprenor-

phine¹⁸⁻²⁰, which is used in therapy substitution programs for dependent patients, as well as from methadone^{5,14-17} and morphine²⁷, which are also used frequently in therapy substitution programs for opioid-dependent patients¹ (Table II). The evidence related to buprenorphine is limited. Navkhare et al²⁰ described the case of a patient with psychotic symptoms (referential and persecutory delusions) and visual hallucinations, but with normal sensorium, after abruptly stopping buprenorphine treatment. The patient had no family history of any psychiatric disorder or diseases, including psychotic spectrum disorders. Symptoms remitted with the reintroduction of buprenorphine. He was being followed up and had no recurrence of psychotic symptoms for the last 6 months while continuing to be on a tapering dose of buprenorphine (currently 4 mg). Weibel et al¹⁹ described another case report of a patient who displayed psychotic symptoms (mystical and paranoid delusions, auditory hallucinations), suicidal thoughts and anxiety, 2 weeks after buprenorphine withdrawal. The authors discuss how the delayed onset of psychotic features is most likely related to the medication's long half-life (40 h). Also, Karila et al¹⁸ presented a case of a patient who developed visual and auditory hallucina-

Table II. Psychotic symptoms following buprenorphine, morphine and methadone withdrawal.

Authors	Year	N	Drug	Withdrawal symptoms	Evolution
Navkhare et al ²⁰	2017	1	Buprenorphine	Referential and persecutory delusions along with accompanying visual hallucinations. There was no evidence of delirium.	The patient began with these symptoms after abruptly stopping buprenorphine. Treatment with olanzapine did not fully eliminate the symptoms. He was restarted on buprenorphine 2 mg twice a day, and symptoms remitted within the next 48 hours.
Weibel et al ¹⁹	2012	1	Buprenorphine	Mystical and paranoid delusions and intense auditory hallucinations. Suicidal thoughts and intense anxiety.	Symptoms began 2 weeks after he abruptly discontinued buprenorphine (dose 8 mg/dl). Buprenorphine was restarted at 8 mg/d which allowed a complete remission. Complete remission was not achieved with risperidone.
Karila et al ¹⁸	2007	1	Buprenorphine	Anxiety, myalgia, sleep disturbance. Visual and auditory hallucinations, paranoid ideation, alternating phases of agitation and prostration	This patient had been receiving 6 mg/day of buprenorphine, and 3 days after reduction of buprenorphine the symptoms described appeared. The introduction of loxapine only improved the symptoms partially. Reintroduction of buprenorphine at 6 mg/d made the symptoms disappear.
Aiyer et al ²⁷	2017	1	Morphine	Disorganized thinking. Delusional thoughts. Paranoia. Auditory and visual hallucinations.	Psychotic symptoms appear after morphine administration and disappear with oxycodone 10 mg every 8h.
Sutter et al ¹⁷	2017	1	Methadone	Formal thought disorder Persecutory delusion Acoustic hallucinations	A patient with psychotic symptoms six days after replacing his methadone treatment (180 mg/day) with 120 mg/d of morphine. The symptoms subsided once the methadone was reintroduced.
Cobo et al ¹⁴	2006	2	Methadone	Delusional ideation and other psychotic symptoms	Case reports with symptoms after sudden withdrawal or decrease of methadone
Shreeram et al ¹⁶	2001	1	Methadone	Auditory hallucinations and delusions	Psychosis after ultrarapid opioid detoxification
Levinson et al ¹⁵	1995	2	Methadone	Psychosis	Case reports, where the methadone resumption is required as a treatment
Kumor et al ⁵	1987	1	Methadone	Visual and auditory hallucinations	The patient was treated for cancer and presented mental status alteration after he was withheld from methadone. His mental status improved when he was treated with morphine.

tions, and paranoid ideation, following buprenorphine withdrawal that disappeared only after its reintroduction. After an 8-month follow-up, the patient had no psychotic symptoms but did con-

tinue with buprenorphine, with the same doses as before the episode. However, there is more evidence regarding methadone withdrawal. Sutter et al¹⁷ layout a case report of a middle-aged patient

with a medical record of schizophrenia receiving methadone treatment. Due to the QT-prolongation she presented, the patient changed treatment (methadone to morphine). Even though she did not have withdrawal syndrome, she did have persecutory delusions and acoustic hallucinations, she was very irritable, and had psychomotor agitation. These symptoms remitted after reintroducing her previous treatment. Shreeman et al¹⁶ also described the case of a patient who was receiving maintenance therapy with methadone. She underwent ultrarapid detoxification. One day before detoxification, a urine screen was positive for methadone. She became agitated during extubation and presented psychotic symptoms (auditory hallucinations and delirious ideation) despite being oriented. Psychotic symptoms disappeared after 24 hours. Additionally, Levinson et al¹⁵ compared 2 patients with methadone withdrawal psychosis in which the methadone is considered an additional treatment to the neuroleptic in one case. However, the psychosis was spontaneously resolved in the other case, and none of them had a typical withdrawal syndrome. Cobo et al¹⁴ also described 2 patients with the same features who needed reintroducing the previous long-term maintenance treatment with methadone. Kumor et al⁵ also described a case report of a patient with cancer that presented psychotic symptoms following the withdrawal from methadone used as a painkiller. As small amount of evidence is described with morphine treatment. Aiyer et al²⁷ described a patient treated for chronic back pain with an intrathecal morphine pump for several years. The patient spontaneously started to experience psychotic symptoms. Studying the intrathecal pump's performance, it had stopped running; thereby, it was not delivering intrathecal morphine. After opioid rotation with the administration of oral oxycodone, the patient's psychosis improved drastically within a few days.

Opioids and Heroin

We describe the evidence of psychotic symptoms following the withdrawal from opioids. Although it is not clear which opioid the sources are referring to, it seems that it could mainly be heroin^{8-10,21,28,29} and in some cases, it is clearly described as heroin^{10,30}. Many articles were discarded due to the multiple studies on the relationship between opioid intoxication and psychosis or psychotic symptoms (Table III). We specifically outlined methadone withdrawal inside the opioid group. Some authors reported mixed affective

and psychotic symptoms. Shariat et al⁹ published a retrospective study that focused on possible bipolar onset related to withdrawal among opium users, suggesting that people who have developed manic episodes after opioid withdrawal might have been genetically predisposed to bipolar disorder.

Furthermore, Khalili et al⁸ reported a case series of nine opioid-dependent patients with hypomanic symptoms, which reverted in most cases when they started retaking the opioid. Similarly, Sivolap et al²⁹ showed the same resolution in patients that presented psychotic symptoms with delusions. Even though Lejoyeux et al²¹ did not describe psychotic symptoms, they did describe depression. It is considered essential to include the psychiatric symptoms withdrawal can induce and consider the elevated suicide risk it entails. Other authors clearly described psychotic symptoms that could be related to schizophrenic diseases²⁸. Regarding heroin withdrawal, Rovai et al³⁰ described symptoms that can be compared with clinical manifestations of schizophrenia, emphasizing how heroin can be considered a treatment due to the tropism for the dopaminergic system. In addition, Sullivan et al¹⁰ presented a middle-aged heroin-dependent patient who developed new-onset mania, increased energy, decreased sleep, and pressured speech plus auditory hallucinations, ten days after the heroin detoxification and subsequent maintenance of the opioid antagonist naltrexone.

Discussion

The relationship between substance use disorders and psychosis is still not clear, especially when it comes to the study of opioid withdrawal and its consequences, including new-onset mania and mixed affective and psychotic symptoms¹⁰.

This review describes published evidence that discusses the relationship between the new onsets of psychotic symptoms due to different opioid withdrawals. Although results show different symptoms, there is still no clear definition of them or the possible risk factors that a patient can have when they undergo detoxification treatment. Additionally, we have not found a correlation between gender and opioid withdrawal and psychosis⁶.

Closely related to the psychotic symptoms induced by opioid withdrawal, an amotivational syndrome³⁰ described as the state every heroin

Table III. Psychotic symptoms following heroine and opioids withdrawal.

Authors	Year	N	Drug	Withdrawal symptoms	Evolution
Shariat et al ⁹	2013	45	Opioids	Manic symptoms	A retrospective study of mania with opioid withdrawal in patients admitted to a psychiatric hospital in Iran during a 3-year period
Khalili et al ⁸	2012	9	Opioids	Hypomanic symptoms	Case series of opioid-dependent patients. Patients displayed pure or mixed hypomanic symptoms during opioid withdrawal.
Sivolap et al ²⁹	2003	377	Opioids	Acute psychosis of delirious structure	Clinical study of opioid dependent patients who presented psychosis manifestations after the withdrawal period.
Lejoyeux et al ²¹	2000	n.a.	Opioids	Affective symptoms: depression	Psychotic disorders in opioid-dependent patients can be induced by withdrawals. These psychotic disorders are more often described after opioid (methadone) discontinuation.
Pérez de los Cobos J et al ²⁸	1987	4	Opioids	Psychotic symptoms	Patients who presented psychotic symptoms after the opioid withdrawal who were diagnosed of schizophrenia.
Rovai et al ³⁰	2013	n.a.	Heroin	Amotivational syndrome	Related to the post-withdrawal syndrome (PWS) as an enduring pathologic state in abstinent detoxified opioid addicts.
Sullivan et al ¹⁰	2005	1	Heroin	Bipolar diathesis and auditory hallucinations	It suggests that after heroin detoxification and/or naltrexone maintenance, the patient manifested the psychotic symptoms.

n.a.: Not applicable.

addict goes through. It focused on the detoxification cycle when the patient goes from an acute to a chronic heroin withdrawal state, in which the patient develops hypophoria with somatic and mental symptoms.

In this revision, we found a majority of case reports which describe psychotic symptoms. Most of the articles discussed are case reports that describe symptoms that appear after the suspension of the opioid. These psychotic symptoms disappear after the reintroduction of the same or another opioid, and in some cases, with antipsychotic treatment. It seems that the time association is present in all of them: symptoms appear days after the interruption of the opioid. However, as for systematic reviews, the literature is scarce, and we mainly found case reports or case series including 169 patients.

Some patients referred mainly visual hallucinations^{12,13,18,20,27}; and auditory hallucinations^{10,13,16-19,27}. However, this was not displayed

in all the cases, so they are not core symptoms. Visual hallucinations could be symptoms < limitation in this study. It should be considered that unusual symptoms may be related to the withdrawal of their pain treatment⁵.

It has been proposed that the comparison between different drugs such as cannabis, amphetamines, cocaine/crack, and opioids appear to be linked to a reduced risk of psychosis³¹. The prevalence of psychosis is higher than expected in the opioid substitution treatment¹. The reintroduction of the opioid stopped the psychotic symptoms. However, in several cases, the symptoms were resolved after reintroducing the opioids, which were added to the patient's neuroleptic treatment¹⁸⁻²⁰. The majority of the authors reported that the psychotic symptoms appeared very close to opioid withdrawal and improved with their reintroduction^{5,14,15,17,27}. It has been suggested that opioid agonists could have antipsychotic effects⁶. It could be based on the evidence that long-term

methadone treatment could prevent relapse in patients who have already had a psychotic episode or are diagnosed with schizophrenia⁶. Other studies support the possibility of the antipsychotic effects of opioids like methadone^{7,22-24}. Schmauss et al²⁵ proposed analyzing the antipsychotic potency of the partial opioid agonist buprenorphine based on 10 neuroleptic-free schizophrenic patients suffering frequent hallucinations, delusions, and severe thought disorders. Buprenorphine had a pronounced antipsychotic effect, which lasted about four hours, in 7 of the 10 patients with schizophrenia. Only in those 3 patients who had residual symptoms was buprenorphine ineffective. These preliminary findings indicate that opioids have an antipsychotic effect in patients with non-residual schizophrenia. Brizer et al²⁴ describe methadone used as an add-on treatment in 7 patients, which was successful in 4 patients. Also, Feinberg et al⁷ described the case of a patient with a diagnosis of schizophrenia who was in a methadone maintenance program. He was suffering auditory hallucinations and was treated with neuroleptics, but he did not tolerate these drugs' extrapyramidal side effects. Due to this fact, it was decided to increase methadone (as the only antipsychotic), and his psychotic symptoms improved noticeably. Additionally, methadone use has also been described in 114 patients as an adjuvant drug to the antipsychotic drugs to reduce the antipsychotic dosage and side effects²². Sobih et al²³ proposed methadone as a treatment in 7 cases of resistant paranoid schizophrenia who showed significant improvement. Walby et al³² presented the treatment of 4 opioid-dependent psychotic patients with methadone and antipsychotic medication. All of them improved after the introduction of the methadone treatment.

Furthermore, Shariat et al⁹ put forward that opioids might act as mood stabilizers. In opioid-dependent patients, this consumption could prevent mania from developing, so withdrawal can act as discontinuation of a mood stabilizer in a subject predisposed to bipolar disorder. Therefore, opioids could mute threatening mood states. As known, one of the uses of morphine could be to control agitation. Comfort et al³³ raised the possibility of morphine as an antipsychotic agent, pointing out the difficulty of proving this theory with research. Morphine congener or morphine precursor is proposed to significantly enhance clinical outcomes of schizophrenic outpatients treated with standard dosages of atypical or typical antipsychotic agents³⁴.

We found as limitations that most of the articles are case reports and case series. In addition, we cannot affirm the temporal causality in all the reports, and there were other influencing factors. Moreover, many reports are not clearly defining which kind of opioid is causing the symptoms, so based on the data obtained and the history of opioid intake, it was presupposed that in many cases, the opioid that was being considered was heroin. However, we reviewed all the published papers on PubMed related to this topic, and we have added other papers related to this topic from other journals.

It is essential to consider opioid withdrawal in the differential diagnosis of patients presenting psychosis in similar clinical conditions. If needed, aside from the antipsychotic treatment, it is critical to consider the possible replacement or re-introduction of opioids to prevent further deterioration in the patient's mental status¹⁷. In complex cases of a schizophrenic patient with substance use, research is necessary to clarify the role of opioids as a potential antipsychotic treatment.

Conclusions

This study encompasses a comprehensive description of the literature concerning the possible unknown outcome of opioid withdrawal. There are 7 reports of temporal association between withdrawal and psychotic symptoms that improved after the reintroduction of the opioid. There is moderate evidence of the sedative effect, and it could have an antipsychotic effect and exacerbate the affective symptoms due to the mood regulation in the endogenous opioid system. This fact should be considered in the clinical practice if we consider that opioid detoxification may unmask an underlying psychotic state in patients with a high risk of presenting psychotic symptoms or even developing chronic psychosis or schizophrenia.

Conflict of interest and Source of Funding

Dr. Maria Teresa Lozano-López has received fees to give lectures from Lundbeck and Dr. Sinta Gamonal-Limcaoco has received fees to give lectures from SANOFI. Dr. Nerea M. Casado-Espada has received an economic award from Janssen in an oral communication contest and has received SANOFI lecture fees. Dr. Begoña Vicente-Hernández has received fees to give lectures from Lundbeck and Janssen-Cilag. Dr. Lara Grau-López has received fees to

give Janssen-Cilag, Lundbeck, Indivior, Otsuka, Exeltis, and Gilead lectures. Dr. Carlos Roncero has received fees to give lectures from Janssen-Cilag, Ferrer-Brainfarma, Pfizer, Indivior, Lundbeck, Otsuka, Servier, GSK, Rovi, Astra, Gilead, MSD, Sanofi, and Exeltis. He has received financial compensation for his participation as a board member of the Janssen-Cilag, Lundbeck, Gilead, MSD, Mundipharma, INDIVIOR, Exeltis and Martindale board. He has participated in the PROTEUS project, which was funded by a grant from Reckitt-Benckiser/Indivior. He received two medical education grants by Gilead. For the remaining authors none were declared.

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