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Letter to the Editor

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## Methadone: A Fast and Powerful Anti-anxiety, Anti-depressant and Anti-psychotic Treatment

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TO THE EDITOR: On the brink of retirement, I find it useful to raise certain important points about the treatment of drug addiction, most particularly the observation that methadone exercises fast and powerful anti-anxiety, anti-depressant and anti-psychotic effects.

For 30 years, with my colleagues at the Phénix Foundation - now 60 in number - we have followed more than 2000 heroin addicts. We have often been surprised by the almost miraculous action of methadone in stabilizing important psychiatric disorders that had responded poorly to medication such as antipsychotics and to psychotherapy. To illustrate this observation, I present four particularly interesting clinical cases.

During the Seventies, most heroin addicts were still socially integrated, intelligent and cultivated people, in search of new sensations through opiate use. This was perceived as a sensorial search, an exploration of pleasure, a semi-mystical enlargement of awareness within a private and elitist sphere. Trapped by heroin, with their autonomy and quality of life threatened by their dependency, these addicts sought out substitution treatment. Many among them were subsequently able to wean themselves off methadone, successfully and without relapses, after a few years of medical and psychosocial treatment. Part of this success must, of course, be attributed to what was often a fairly solid personality structure and a favourable psychosocial environment.

Sadly, owing to the ever-increasing prevalence and profitability of drug trafficking, heroin is now

available at every corner of town. Its most powerful impact has been on the more fragile among our young people, those with affective, social and psychiatric problems. Suffering its side-effects, these unfortunates have spontaneously discovered ways to alleviate their pain, first through nicotine, alcohol, benzodiazepines and opiates, then, more recently, through cocaine. All of these substances increase the concentration of dopamine in the brain, to different degrees and in different ways [15].

A number of studies postulate that genetic particularities in certain individuals lead to a dysfunction of dopaminergic systems owing to an insufficient number of dopamine receptors or an excess of 'recapture pumps'; this might explain certain psychological disorders such as attention deficit hyperactivity disorder (ADHD). When a cocaine addict says he takes the drug in order to be calm and concentrated, ADHD is sought out and is nearly always found.

By using the 15-question Connor test, we have evaluated the severity of ADHD symptoms in 371 of our patients in methadone substitution treatment. What emerged was a marked over-representation of symptoms in our population, including 25% hyperactivity compared to the 5% norm. The hyperactivity group, compared to the non-hyperactivity group, proved to have twice as many problems with the police and to use double the amount of heroin before treatment (3 grams per day).

We also divided patients into groups according to

their degree of pathology, and found that the group with the highest psychiatric comorbidity used double the amount of heroin before treatment (2.9 grams per day compared to 1.4 grams per day) and had suffered seven times more overdoses.

When one prescribes morphine to a normal individual in care, even over a long period of time, not only does the person feel no particular pleasure, but also often suffers disagreeable side effects, such as nausea. When treatment ends, the person does not become an addict.

The same can be said of thousands of American soldiers who became heroin addicts in Vietnam owing to the availability of the drug, the need to compensate for factors such as combat stress and their distance from loved ones. Once home, back in reassuring and affectionate surroundings, far from military conflict and, most importantly, sheltered from the drug, a majority of the soldiers remained abstinent. Among those that continued heroin use in America and remained addicted, severe psychiatric comorbidity or psychosocial complications were often observed.

Based on our longstanding clinical experience and numerous evaluations, we have concluded that the most important factor — the factor best correlated with addiction development, maintenance and treatment failure — is the presence of psychiatric suffering accompanied by psychosocial complications [16, 17, 33].

Numerous recent studies inquiring into the origins of psychiatric disorders have shown, more often than not, an important genetic and neurobiological component. In this case, psychiatric difficulties come to the surface, in different forms, as early on as childhood. They entail numerous affective, social and psychological complications. If the hypothesis of a primary neurobiological disorder is confirmed for these patients, it is understandable that medication specifically balancing cerebral dysfunction is more efficient than psychodynamic treatment alone.

In such patients, psychiatric suffering is not always conscious and may often be denied, but the first time they take an opiate, it will emerge, and leave an indelible mnemonic impact. For the first time in their lives, these patients will feel well, 'feel normal', as an ordinary person would put it. They then realize that they have been suffering for many years, without ever knowing what it is like to be normal. They will then naturally seek to reproduce and maintain this state of equilibrium, but at the cost of risking chronic addiction. In these cases, any weaning attempts are bound to lead to the reappearance of underlying psychiatric disorders.

It is like the experience of a short-sighted child, who thinks his blurred world is normal, but, on discovering glasses during adolescence, discovers the pleasure of precise and colourful vision. He will never want to go

without glasses again.

Such is the problem of substitution treatment in many cases where the patient is one who suffers from a chronic disorder, most often triggered by a dysfunction of one or many neurobiological cerebral systems, due to genetic factors and aggravated by an abuse of drugs that permanently modifies the functioning of the brain [18,19,21,26,32].

The search for drugs to alleviate psychological suffering has been well documented over the last decade [2,5]. As early as 1970, studies refer to this concept of automedication to explain the use and maintained use of drugs. Numerous observations have described the calming and stabilizing virtues of opiates in aggressive or psychotic patients and in those with bipolar disorders [11,13].

Published research showed spectacular improvements in non-addicted patients with paranoid schizophrenia who had not benefited from the effects of the usual anti-psychotic treatment [1,3,28].

Other studies made over a long period have demonstrated the marked anti-depressant effect of methadone in patients with depression who were resistant to the more usual anti-depressants. One must recall that opiates, especially laudanum, were used at the beginning of psychiatric history to treat severe forms of depression such as melancholia and manic-depressive psychoses [5,7,10,24,25,29].

During a trip to study drug problems on the paths of Kathmandu in 1970, I was impressed to see travellers successfully using a little opium to treat young people in complete delirium after they had taken LSD.

The anti-anxiety effect of methadone is widely recognized. Methadone blocks the stress hormone at a cerebral level, which allows severe anxiety states to be durably stabilized. Conversely, the interruption of methadone treatment entails a dysfunction of the stress axis, and leads to long-term anxiety disturbances.

How can the speed and efficiency of the anti-anxiety, anti-depressant and anti-psychotic action of opiates and methadone be explained? The very little research carried out so far leaves scope for an explanation. The effect is probably due to complex interactions between endorphinic, dopaminergic and glutamatergic systems [6,12,22,23,27,30]. Quite a few studies have demonstrated the anti-depressant effect of NMDA receptor agonists in animals [8,14].

In 2004, Sanacora and colleagues found significantly higher levels of glutamate in the occipital cortex of 29 patients with major unipolar depression, when compared with 28 control subjects. One explanation for mood disorders would therefore be the dysfunction of the glutamatergic system. On this view, antagonist substances of the latter would have anti-depressant effects.

Very recently, in August 2006, Carlos Zarate and colleagues [34] published a study that showed a marked and speedy anti-depressant effect following a single dose of an NMDA antagonist, Ketamine, in patients with major depression disorders. This anti-depressant effect was present among some as early as two hours after the Ketamine injection and remained significant throughout the next seven days.

Buprenorphine, an opiate agonist-antagonist, at an adapted dose, has also shown anti-depressant, anti-dysphoric and anti-psychotic properties. An agonist action on the Kappa receptors has been hypothesized in order to explain this psychotropic effect [4,9,31].

The remarkable progress made over these last few years in the field of animal research, cerebral imagery and the neurosciences should enable us to find further answers to this fundamental question.

One can only hope that research will lead to the development of new and efficient medication able to offer patients suffering from addiction better stabilization.

In order to illustrate the anti-anxiety, anti-depressant and anti-psychotic effect of methadone, I will now present clinical cases summarizing the treatment of four patients suffering from significant psychiatric comorbidity. In all four cases, methadone demonstrated remarkable success in stabilizing the patient.

### **Case David**

An occasional hashish smoker, the 22-year-old David was discovered in a city park stark naked and masturbating. Taken to the psychiatric hospital, he exhibited a hypermanic state which evolved to the frankly manic. Bipolar disorder with psychotic characteristics was diagnosed and Haldol (200 mg by injection) prescribed. When discharged, he was given a prescription for 10mg per os of Haldol daily.

Suffering from the side-effects of neuroleptics, he discovered one day that he felt much better psychologically if he took heroin. He stopped taking Haldol and developed a rapid dependence on heroin, graduating to injection. After a few months of submission to heroin, he successfully undertook a first methadone cure of one full year, remaining well balanced on the psychological level. At 28, eager to live normally and without drugs, he decided to end methadone support. One month later, a new manic episode occurred, and as a result he lost his job. He started self-medicating with heroin again, in a major way, and stabilized on the psychological level, but with many financial and legal disadvantages. That is why he decided to take a long-term methadone cure with a private doctor.

Over six years, with a dosage of 100mg of methadone per day and without any other drug, he remained perfectly stabilized on the psychological level, enjoyed

a good quality of life, worked regularly and got married.

In 2002, he became an administrative civil servant, working in a government building very close by our treatment centre. He transferred the responsibility for his treatment to us and we continued his dosage of 100mg per day. He continued to be very well stabilized in his mood.

One year later, again very eager to live without chemical help, he insisted on being progressively weaned off the treatment. I set out to discourage him reminding him about the events that had lead up to his first psychiatric hospitalization when he was only 22. He minimized their importance and persisted in his idea. Over the next months he steadily reduced his dosages. Three years later, when it had reached just 20 mg, I got a telephone call from David's boss. He was extremely concerned. David, in a half-naked state, had made sexual advances to a secretary, tried to buy an elephant over the telephone and otherwise behaved in a generally agitated and incoherent manner. It amounted to a manic decompensation — all his defence mechanisms had collapsed so completely that, for the first time in many years, I had to organize his urgent admission by ambulance to a psychiatric hospital. The scandal was great, since David had a service apartment in the building itself and was entrusted with confidential assignments.

Even after treatment at the psychiatric clinic with 100mg of Depakine and neuroleptics, he remained agitated and threatening. Finally, the psychiatrist treating him agreed to re-establish an adequate methadone dosage — 50 mg — and the patient quickly and successfully restabilized.

Over the last three years, first in monotherapy with methadone, then with MST (slow-release morphine tablets) because of certain methadone side-effects — sweating and oedema — he has been able to lead a normal life, maintaining a satisfactory level of mood stability. We were able to save his job by explaining to his employers the exceptional character of his outbreak, related to the fall in his methadone dosage, just as surely as an epileptic would collapse into crisis if dosages of his stabilizing medication were to fall below a certain level. He is now holding down his job to the complete satisfaction of his superiors, besides practising several sports and other leisure activities.

He now accepts his need to take a daily opiate dose for the rest of his life. In the long run he is proving much more stable, enjoying a better quality of life and experiencing far fewer side-effects than do bipolar patients treated with classic medications.

## **Case Alain**

Alain has been a heroin addict since he was 17. Psychiatric antecedents were found in his family. After some attempts at weaning him off the habit failed, he began a methadone treatment with us when he was 22. During the early years, dosage was limited to between 20 and 50mg, the result being that he continued to take heroin once or twice a week, in spite of the psychosocial support he was receiving.

He then agreed to accept an increased dosage of 120mg of methadone. From then on he remained completely abstemious by maintaining good psychosocial balance and holding down a stable job.

One day he decided to wean himself progressively off methadone and left soon afterwards to spend some weeks in Crete with his girl-friend. When the time came to return to Switzerland, he vanished at the airport and his friend had to come back without him. He was found several days later wandering around the island, half-naked and confused, in a disturbingly paranoid psychotic state. He saw the sea as totally black, bubbling with a multitude of crabs ready to attack him. Once he was back in a psychiatric hospital, he spent several weeks under treatment with neuroleptics, showing only feeble signs of improvement.

On being discharged, he relapsed immediately into heroin addiction, with a clear increase in his psychiatric disorders as a consequence. Following this relapse, he returned to us again to follow a methadone treatment that would be appropriate to his needs. He stabilized perfectly in three days and remained so for several years, maintaining normal regular working habits and leisure activities.

In 1987 came another relapse, when he cut his methadone dosage to 50mg — with destabilizing results — and started taking cocaine. One Thursday afternoon, I was at home when I was warned that the burglar alarm had gone off at our clinic. When I arrived on the spot, I saw that the glass outer door had been smashed in and that Alain was hacking the furniture to bits with an axe. I firmly asked him to hand it over and he did so without argument. He was in a full psychotic crisis, confused, no longer able to remember that the centre was closed on Thursday afternoons. I called an emergency ambulance and he was again taken to a secure psychiatric ward. He restabilized in a few days with the appropriate dosage of 120mg of methadone, without neuroleptics. For almost 20 years now, Alain has continued his daily treatment with an adequate quantity of methadone. He continues to abstain completely from drugs. He is married and works full time, to the complete satisfaction of his employers. An HIV-seropositive of long date, he has looked after himself carefully, so much so that he has been able to father a seronegative

child. As a result, he is able to lead a normal family life; he enjoys his leisure hours and a good quality of life. He now realizes the importance to him of keeping to a long-term treatment plan.

## **Case Christian**

Christian's parents divorced when he was six years old. His mother suffered from serious chronic depression and made several suicide attempts. Christian started to sniff heroin when he was 16 and rapidly developed dependency. For three years he alternated outpatient and inpatient weaning processes, with immediate relapses into heroin addiction. At 18 he was hospitalized with septicaemia, arising from an abscessed vein. At 19 he was hospitalized for the first time in a psychiatric ward for a depressed and anxious condition displaying problems of a psychotic nature. After this episode, he spent two years in a home for adolescent boys before relapsing into heroin addiction.

It was here that he first requested help from us, and it was then that a serious burden of psychosocial responsibility descended on our shoulders — and has remained there up to the present day. In the early years he refused to accept the increases in methadone dosages we recommended, took only inadequate amounts and even then took them only irregularly. He behaved in the same way with the antipsychotic medications we were obliged to prescribe for him. This disobedient behaviour partially explains why he was hospitalized eight times with psychiatric decompensations up until 2003.

At 24, he was living alone, turned in on himself. He was found on private property. He broke into the houses of strangers, slept in their beds and used their showers. Several times he smashed down his mother's door while she was out, on the pretext that he was hungry. At the psychiatric hospital he was diagnosed with intense psychotic problems — polymorphous and schizophrenic in nature. He fled from the clinic and was found wandering barefoot in the countryside, beset by auditory hallucinations.

Rehospitalized, he underwent crises of violence and needed to be injected with neuroleptics.

During his sixth psychiatric commitment, owing to his pathological wandering, he set fire to his room. Some time later, he turned up in Zurich, where he committed burglaries — and set fire to his hotel room. He was committed on the spot before being readmitted to the psychiatric clinic of Geneva.

It was at this time that we persuaded him to increase his methadone dosage to 120mg and, especially, to take his neuroleptic medication (Risperdal, 4mg) more regularly. To achieve this we also persuaded him to take it in liquid form, after putting it in his methadone bottles.

In this way he was stabilized on the psychiatric level for a year or two. But in Summer 2003, when he left for a week's holiday in Majorca, he forgot his bottles of "Methadone/Risperdal". He compensated with alcohol and cocaine. When he returned to Geneva, in a semi-maniacal state, he presented himself at his mother's door half-naked and, pushing her towards the bedroom, insisted that he wanted to have sex with her. Confronted by her refusal, he started to strangle her, telling her to "Die". Hearing her screams, the neighbours intervened to save her. Christian was immediately arrested for attempted murder.

The resumption of an adequate intake of methadone and 4 mg of Risperdal made possible the rapid stabilization of his psychological state. The psychiatric reports confirmed the psychotic disorders and the psychiatric decompensation caused by his failure to take methadone. The judge declared him irresponsible, without penal judgment, but with the obligation to have a daily consultation at our centre for the controlled administration of methadone and Risperdal. For the last three years, with our assumption of intensive responsibility — medical, social and psychotherapeutic — Christian has remained well stabilized, without psychiatric relapses and/or drug-taking. He currently takes 110mg of methadone, to which we add 4 mg of Risperdal in drops. He has been able to retake a carpentry training course in a readjustment centre. He has a girl-friend, with whom he lives and has a satisfactory relationship.

### **Case Albert**

Albert's case is a very good illustration of the need for adequate dosages of methadone, and particularly for its regular administration in cases of serious psychiatric comorbidity underlying heroin addiction.

I first met Albert when he was 14, at the psychiatry unit for adolescents where I was working as a doctor. His father was being treated with drugs such as lithium for a bipolar disorder. Albert very quickly presented behavioural problems and anxious-depressive states. He already smoked hashish quite regularly and rapidly developed heroin addiction by the time he was 15. More than once he cut his veins at home. On several occasions he saw us arrive in all urgency at the call of his parents; he ran away each time, and we had to run after him to ensure he did not fall under a truck. He was first hospitalized for psychiatric reasons at the age of 16.

Following thefts of money and cars, driving without a licence and causing accidents, the judge dealing with minors ordered him to be placed for six months in a secure centre for adolescents. He escaped in search of heroin. The institution's psychiatrists were the first to hypothesize that he might have a psychotic personality

structure; they placed him under clinical observation.

Upon discharge from the centre, he relapsed into serious heroin usage and made several unsuccessful efforts to wean himself off the drug with the help of various doctors and specialized institutions. Because of these failures he decided to return to his family in Italy. Once there, however, he dived back once more into heroin use — to a disturbing degree. As a result of an overdose, he was committed for two years to the care of a specialized therapeutic community.

On leaving this centre, he fell back immediately into heroin use and became involved in the business of drug dealing. He was discovered unconscious in a toilet on the Milan-Lausanne train, his pockets packed with drugs. He was sent to prison. When released, and after a new and serious relapse into drugs, he asked to be placed under our authority and in our long-term medico-social methadone programme. He rapidly stabilized with an average dosage of methadone, and followed the course of treatment in the most exemplary way for over four years without any recourse to drugs. It was not even necessary to provide any major psychosocial support — within a few weeks he had got himself a job as a qualified salesman in a luxury Geneva jewellery store. He worked to the complete satisfaction of his boss. He enjoyed a good quality of life. He found a girl-friend who eventually became his wife.

At the end of these successful four years, wanting to live free of any medication, even a safe substitute, he insisted on weaning himself off methadone, something he achieved in a few months. As a post-cure, he went to visit his divorced mother in Italy. Once back there, he felt bad about himself, very anxious and depressed, finding great difficulty in attention and concentration; he nearly killed himself in a collision with a truck.

His mother encouraged him to return to Geneva and resume his course of treatment with us, in order to recover a good level of psychological stability. He did so. Under methadone he quickly became stable again, worked regularly and married his girl-friend.

However, two years later, he once again wanted to quit using methadone and things went wrong very quickly. Some days later, he sprayed phallic images on the walls of his apartment, set fire to his posters, fired an air-rifle at his wife and shut himself in his room after swallowing two bottles of tranquillizers. When taken urgently to hospital for treatment, he worked himself into an extreme fury a few hours later and broke everything within reach. Once again he had to be committed to the Geneva psychiatric clinic, where he was kept for a month, under neuroleptic treatment.

Once out of the clinic, he still felt unstable and, to return to a condition of normality, he wished to resume his treatment with us. We discovered once again how quickly he could return to working regularly and leading

a stable life. He followed the treatment for three and a half years without any heroin; he was perfectly stable, working well with little interruption.

Then again he decided he wanted to reduce his dosage of methadone, despite all our endeavours to dissuade him. His condition deteriorated rapidly, but he refused to go back to a higher dosage of methadone. Similarly, he refused to be hospitalized, on the grounds that the doctors of the time refused to prescribe methadone and because of his past bad experience with neuroleptics.

A few days later he failed to come to take his methadone for fear of being poisoned. That evening, in a disturbing psychotic condition further aggravated by heavy drinking, he set fire to his apartment and wandered aimlessly around the city. After being arrested the next day, he masturbated in front of the police. Once again he was committed to the psychiatric clinic, this time in a near-catatonic condition. When released after several weeks of treatment, he decided to go to stay with his father, who had settled down in Rolle, a village between Geneva and Lausanne. After being completely weaned off methadone, responsibility for him was taken by the psychiatrists of the nearby psychosocial centre of Prangins, who decided on treatment by classical means.

Six months later he returned to see me in Geneva. He was in a disquietingly psychotic state, delirious and presenting all the usual signs of schizophrenia. For this reason he was once again hospitalized in a psychiatric clinic, but this time in Prangins, near where he was then living. There he was scheduled for several months of treatment with neuroleptics by injection, because the medical management of the clinic refused to consider any prescription of methadone.

One month after his discharge from the psychiatric clinic he saw me again, showing severe instability on a psychological level and presenting a disturbingly risky forms of behaviour. As it happened, over the previous few weeks, he had injected himself with air, then with mercurochrome. He had shared syringes to inject himself, so running a high risk of infection with AIDS; even more seriously, he had suffered two overdoses which had called for emergency resuscitation at Nyon hospital.

Because of the high risk of death faced by this patient and because of his psychotic state and despite the refusal of the psychiatrists at Prangins — who had told him that if he returned to methadone they would no longer treat him — we decided to take him back on the understanding that he would take a small methadone dosage.

With a first dosage of 30mg, which was progressively increased to 50mg, Albert once again regained psychological stability almost immediately and within a few days was able to return to work.

To save Albert having to travel daily between Rolle

and Geneva to get his dose of methadone, we arranged for him to be taken on as a patient by a local doctor, a general practitioner in Rolle.

After one or two problem-free years, tragedy intervened. Albert's doctor gave him a full week's series of methadone doses to cover the Easter holidays. Albert mistakenly took one or two doses ahead of schedule and, in the absence of his doctor, filled the two-day gap with alcohol. In this state he fired his air-rifle at some street signs. Arrested by the police, he was once again committed to the psychiatric clinic at Prangins. As the medical management of the clinic refused to consider any prescription of methadone, he was treated by more classic methods and was left in an open ward. It is hardly necessary to say that withdrawal from methadone brought on a rapid and serious psychiatric decompensation. He fled from the clinic, took his car and knocked down a passer-by — not fatally. Now considered to be a serious psychopath, he was imprisoned. The psychiatric expert came to very negative conclusions, as a result of which he was kept in jail for a number of years. Immediately after leaving prison, he died of an overdose.

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#### **Contributors**

The authors contributed equally to this work.

#### **Conflict of Interest**

The authors have no relevant conflict of interest to report in relation to the paper.

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