Research report

Cocaine abuse and the bipolar spectrum in 1090 heroin addicts: Clinical observations and a proposed pathophysiologic model

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Abstract

Background: Several studies indicate a specific relationship between bipolar disorder and stimulant use and abuse. It has generally been assumed that cocaine use represents self-enhancement or attempts to optimize one’s level of hypomania, cyclothymia or hyperthymia. This topic required further examination among heroin abusers because cocaine abuse is commonly comorbid with heroin abuse.

Methods: Cocaine abuse by bipolar subjects was investigated in a group of 1090 treatment-seeking heroin addicts enrolled between 1994 and 2005. We collected data with 1) the Drug Addiction History Rating Scale; and 2) the Semi-structured Interview for Depression, which inquires systematically among others, about hypomania, cyclothymia, hyperthymia and depressive temperament. Subjects were aged 29±6 years, and predominantly male (76.2%).

Results: Univariate and multivariate analyses provided correlations in favour of a link between current cocaine abuse and double diagnosis, with special relevance to the bipolar spectrum, as well as psychotic disorders (p<0.0001).

Limitation: The modality of access to cocaine in different communities and the difficulty to distinguish cocaine use from abuse by the rating scale administered may have limited the interpretation of results.

Conclusions: If cocaine abuse precedes that of heroin or is concomitant, heroin may hypothetically serve as a “mood balancer” which transiently dampens subthreshold excitatory states and mood swings. Our data further suggest the need for a more complex model linking cocaine and bipolarity: subthreshold bipolarity, including hyperthymic and cyclothymic temperaments, seems to predispose to heroin addiction, but craving for the suppressed hypomania in turn could lead to cocaine abuse, which eventually unmask a frank bipolar disorder — in some cases leading to mixed state, severe mania, as well as psychosis beyond mania. Prospective observations would shed further insight on this complex interface of major clinical and public health importance.

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Keywords: Cocaine; Heroin; Bipolar spectrum; Cyclothymia

1. Introduction

Prevalence rates of bipolar disorder of 22% (Mirin and Weiss, 1986) and 30% (Nunes et al., 1989) have been
reported among cocaine users. In cocaine users bipolar disorder is more frequent than MDD or major depressive disorder (30% versus 13%); the rate of bipolarity is even higher if cyclothymia is considered (Weiss and Mirin, 1985; Weiss et al., 1988; Nunes et al., 1989). While such data allow us to state that the prevalence of cocaine use disorders is higher in bipolar subjects than in the general population (Brady and Lydiard, 1992), other authors point out the clinical importance of minor bipolarity (with hypomanic swings or states) in accounting for the high rates of comorbidity in treatment-seeking cocaine abusers (Rounsaville et al., 1991) and in cocaine abusers requesting psychiatric help for minor mood disturbance (Sherwood Brown et al., 2001).

In subjects hospitalized for acute substance-related psychiatric syndromes, comorbid psychiatric diagnoses (assessed in 64.9% of the sample) could be related to individual substances: Specific links between cannabis use and schizophrenia and bipolar disorders and cocaine have been postulated (Andreasson et al., 1989; Zammit et al., 2002; Albanese et al., 2006). On the other hand, heroin use itself was related to the absence of axis I diagnoses and antisocial personality disorder (Karam et al., 2002). Finally, a higher rate of bipolar disorders and anxiety disorders was registered in the subgroup of polydrug abusers compared with single-substance abusers (Skinstad and Swain, 2001).

Given the high prevalence of polysubstance abuse with cyclothyemic and subthreshold bipolar disorders in outpatient (Akiskal et al., 1977) and community (Judd and Akiskal, 2003) settings, we hypothesized that the activities of multiple drug use, with special regard to cocaine use, relates to the extended bipolar spectrum, rather than to full-blown bipolar I disorder. In methadone patients, stimulant use has already been linked to an excess of less-than-mani bipolar disorders (bipolar II and cyclothymic) which were rated as independent double diagnosis (Rosenblum et al., 1999). In our opinion, heroin addicts represent an ideal model to investigate the independent predictors of concurrent cocaine use: In fact, it allows to assess substance-specific correlates beyond risk dispositions to illegal and heavy drug use, which is common to both heroin and cocaine. Moreover, since heroin and cocaine are antagonists to one another in their physiologic properties, this pattern of polysubstance abuse cannot be viewed as the simple enhancement of a causal relationship between substance use and the emergence of certain affective symptoms. Lastly, heroin addicts are themselves a population with an expected concentration of bipolar spectrum disorders (Maremmani et al., 2006) which makes it particularly useful as a substrate to investigate a possible link with cocaine independently of a general proneness to illegal substance use and addiction. It is of historical interest, that when clinicians started using lithium for manic–depressive illness in Italy decades ago, they also considered using it to reduce craving in young drug addicts (see Altamura, 1975). More recent work by the first author and his collaborators (Maremmani et al., 2000, 2003, 2004; Pacini and Maremmani, 2005) provides more extensive documentation of the historic antecedents and current clinical data suggesting that opiates, heroin and methadone, in particular, might possess “mood-stabilizing” properties (Pani et al., 1999). More specifically, heroin might act in the short term as a fast-acting “mood balancing” (sedative, anxiolytic) capacity, but in the long term is likely to be mood destabilizing; whereas long-acting methadone in a proportion of cases could be akin to a “mood-stabilizer” in the long term. This is relevant background for the present investigation on cocaine as a bridge between subthreshold bipolarity and full-blown mania and manic psychosis among heroin addicts.

2. Method

2.1. Sample

The study included 1090 subjects, who had requested treatment during the years 1994–2005 at Drug Addiction Unit of the Department of Psychiatry of the University of Pisa, Italy. All of them received a diagnosis of opioid dependence with physical dependence (according to various DSM criteria) and gave their informed consent for study participation.

The average age of the patients was 29 ±6 years (range 16–51). Most of them were male (76.2%), single (64.4%), with less than 9 years of education (70.7%), and unemployed (39.6%). Socio-demographic characteristics are further detailed in Table 1.

Males and females differed in employment rate (37.7% of males were “blue-collar workers”, 37.4% were unemployed. 23.9% of females were “blue-collar workers” and 46.7% unemployed; df=2; chi 16.61; p=0.0002). Of males 52.1% had “blue-collar worker” parents and 11.8% unemployed parents. Of females 40.5% had “blue-collar worker” parents and 17.4% had unemployed parents (df=2; chi 11.92; p=0.002). 31.5% of males were married versus 47.9% of females (df=1; chi 23.07; p=0.0000). There were no differences between males and females in age, income, education, place of birth or residence, type of accommodation and public welfare benefits.
According to DAH-RS, heroin addicts had cocaine as drug of second choice. Of these 309 (76.5%) were males. Mean age was 29±5. In addition they were characterized by concomitant use of alcohol (57.9%), CNS depressant (52.0%), and cannabinoids (82.7%). Heroin addicts without cocaine use utilize statistically significant less alcohol, cannabinoids and CNS depressant (p<0.05).

### Table 1
Socio-demographic characteristics of the sample (N=1090)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29±6 (16–51)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>831 (76.2)</td>
</tr>
<tr>
<td></td>
<td>Never married</td>
<td>704 (64.4)</td>
</tr>
<tr>
<td></td>
<td>Low (&lt;9 years)</td>
<td>771 (70.7)</td>
</tr>
<tr>
<td></td>
<td>White collar</td>
<td>283 (26.0)</td>
</tr>
<tr>
<td></td>
<td>Blue collar</td>
<td>375 (34.4)</td>
</tr>
<tr>
<td></td>
<td>Unemployed</td>
<td>432 (39.6)</td>
</tr>
<tr>
<td>Income</td>
<td>Poor</td>
<td>182 (16.7)</td>
</tr>
<tr>
<td></td>
<td>In family</td>
<td>994 (87.1)</td>
</tr>
</tbody>
</table>

2.2. Chronology of substance abuse, bipolarity and psychosis

Given the retrospective cross-sectional nature of data collection, we provide what we consider a reconstruction of the age at onset of the different clinical conditions under investigation to the best of our clinical observations. We are doing so to provide the reader with some background to evaluate the timelines for the differential ranges for the onsets of these conditions, which are necessary for the assumptions we make for our proposed pathophysiologic model.

In our sample, patients started using heroin at the age of 18 (range 10–40, [SD=4], mode and median 18), became addicted after a two years’ honeymoon stage (20 years, [SD=4], mode and median 20, range 12–40). Cocaine use similarly started during late adolescence, but the age of onset of cocaine addiction was highly variable with respect to heroin’s, the rule being a heroin–cocaine chronological sequence. Approximately one third of patients became cocaine addicted during treatment intervals between relapses, or during successful treatment program for heroin addiction. The vast majority of our patients were screened for bipolar disorder at time of our baseline evaluation. For some of them, bipolar disorder was ascertained while on treatment, so that the actual prevalence of bipolar disorder may have been underrated for early dropouts. In Italy, at least out of any structured treatment, bipolar disorder tends to be neglected or ruled out by prior clinicians, since substance use is considered a confounding factor, and behavioral aspects of disruptiveness, instability and impulsivity were nearly always ascribed to the addictive lifestyle.

Bipolar disorder would typically set on during substance using periods, while no clearcut major phase had been registered before the onset of substance use (i.e. 18 years). However, we shall point out that a diagnosis of minor, early-onset bipolar disorder is quite unlikely in Italy and would probably be neglected in favour of conduct disorder. Our bipolar addicts, thus, can be regarded as developing full-blown bipolar disorder after becoming occasional substance users, of no specific kind. Since their age at time of study was on average 29, bipolarity seems to have set on typically between 18 and 29 years of age. Moreover, when patients were first enrolled into structured treatment programs (that is at 25 years of age was on average) diagnosis of bipolar disorder was still unlikely, which indicates that the most likely age-range for the first manic or mixed episode is between 25 and 29 for our sample.

2.3. Instruments

Addiction-related information was collected by means of the Drug Addiction History Rating Scale (DAH-RS, (Maremmani and Castrogiovanni, 1989)) administered by an experienced psychiatrist.

This DAH-RS is a multi-scale questionnaire comprised of the following categories: physical health, mental health, substance abuse, treatment history, social adjustment and environmental factors. The specific variables addressed are: hepatic, vascular, haematological, gastrointestinal, sexual and dental pathology, HIV serum-status; awareness of illness, memory disorders, anxiety disorders, mood disorders, aggressiveness, thought disorders, perception disorders; employment, family, romantic involvement, socialization and leisure time, legal problems; use of alcohol, opiates, CNS depressants, CNS stimulants, hallucinogens, phencyclidine, cannabis, inhalants, polysubstance abuse; frequency of drug use, pattern of use, previous treatments; current treatments; methadone dosage. Items are set up so as to elicit dichotomous answers (yes/no).

For the purpose of DAH-RS, psychiatric disorders were investigated on the basis of the DSM-IV Decision Trees for Differential Diagnosis. Each decision tree starts with a set of clinical features. When one of these features is a prominent part of the presenting clinical picture, the clinician can follow the series of questions to rule in or
rule out various disorders. The questions are only approximations to the diagnostic criteria and are not meant to replace them. Three decision trees have been used: “Differential Diagnosis of Psychotic Disorders” (initial clinical features: delusions, hallucinations, disorganized speech, or grossly disorganized behavior); “Differential Diagnosis of Mood Disorders” (initial clinical features: depressed, elevated, expansive or irritable mood; two separate items record the presence of depression and/or any tendency towards the bipolar spectrum as testified by an elevated, expansive or irritable mood); “Differential Diagnosis of Anxiety Disorders” (initial clinical features: symptoms of anxiety, fear, avoidance, or increased arousal).

As for bipolar spectrum diagnoses, histories of previous hypomanic episodes, as well as temperamental characteristics were explored using the criteria listed in the SID, the Semi-structured Interview for Depression (Cassano et al., 1989). All information was gathered from the patient and at least one close relative (usually parents, siblings); in addition, all available clinical records were carefully examined. Inquiry on temperamental attributes was made about the usual self of the patient – during periods free of affective episodes – from patient and significant others. Our operational criteria for affective temperaments represent the University of Tennessee (Akiskal and Mallya, 1987) modification of the Schneiderian descriptions (Schneider, 1958). The SID, developed as part of the Pisa–Memphis (now San Diego) collaborative study on affective disorders, has been used with over 2000 patients at the time of writing: Its reliability for diagnostic assessment of patients and their temperaments has been documented elsewhere (Perugi et al., 1990, 1997). Psychometric validation of the temperament criteria has been subsequently published (Akiskal et al., 1998; Placidi et al., 1998).

Toxicological urine analyses were made by immunoassay method for opioids and cocaine, cannabinoids and central nervous system depressants (unprescribed benzodiazepines). Sample collection was supervised by a nurse in order to prevent fraud. For alcohol we divided patients with and without problematic use of alcohol on the basis of self report, the results of liver function and mean erythrocyte volume, and the ensemble of alcohol-related legal, social and family issues.

2.4. Statistical analyses

We compared heroin dependent patients with and without use of cocaine and other drugs with groups of patients selected on the basis of socio-demographic and clinical variables. The variables that showed statistically significant differences ($p<0.05$) were included in separate logistic backward regression analysis. Statistical analyses were carried out using the SPSS package. Since this is an exploratory study, statistical tests were considered significant at the $p<0.05$ level.

3. Results

Table 2 shows the univariate association between use of cocaine in heroin addicts, on the one hand and socio-demographic characteristics, psychiatric comorbidity, and history of drug addiction on the other (only significant associations are reported).

Table 2
Univariate association between use of cocaine in heroin addicts and socio-demographic characteristics, psychiatric comorbidity, social adjustment and drug addiction history

<table>
<thead>
<tr>
<th>Associated use of cocaine</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N=404$</td>
<td>341 (84.4)</td>
<td>608 (88.6)</td>
</tr>
<tr>
<td>$N=686$</td>
<td>63 (15.6)</td>
<td>78 (11.4)</td>
</tr>
</tbody>
</table>

$T_p$ 4.02 0.044

Living

| In family | 284 (70.3) | 296 (43.1) | 75.26 0.000 |
| Absence  | 120 (29.7) | 390 (56.9) |

Psychotic disorders

| Presence  | 51 (12.6) | 39 (5.7) | 16.1 0.000 |
| Absence  | 353 (87.4) | 647 (94.3) |

Bipolar spectrum

| Presence  | 91 (22.5) | 59 (8.6) | 41.53 0.000 |
| Absence  | 313 (77.5) | 627 (91.4) |

Legal

| Minor/no problems  | 137 (33.9) | 294 (42.9) | 8.51 0.003 |
| Major problems     | 267 (66.1) | 392 (57.1) |

Multiple treatments

| Absence  | 294 (72.8) | 555 (80.9) | 9.76 0.001 |
| Presence  | 110 (27.2) | 131 (19.1) |

$M±SD$ 2.17±1.4 1.15±1.3 11.36 0.000

$M±SD$ 17±4 19±4 $−5.68$ 0.000

$M±SD$ 20±4 22±4 $−5.43$ 0.000

$M±SD$ 90±60 80±60 2.34 0.019

Only significant ($p<0.05$) differences are reported.
Regarding socio-demographic characteristics, only living alone was significantly associated with concomitant use of cocaine in heroin addicts. Other variables such as unemployment, receiving public welfare benefits, coming from white/blue collar or unemployed families, age (less than 25 versus 25 or more years), gender (males versus females), marital status (single versus others), education (less than 8 years versus 8 or more), income (poor versus sufficient) did not prove to be significantly correlated with concomitant use of cocaine in heroin addicts.

As regards psychiatric comorbidity, the presence of double diagnosis, (mood disorders, psychotic disorders and bipolar spectrum), was significantly correlated with concomitant use of cocaine in heroin addicts.

Some aspects of social adjustment, such as work problems, problems in affective relationships and legal problems yielded significant association with concomitant use of cocaine in heroin addicts. Others, like family problems (minor/no problems versus major problems) and leisure problems did not turn out to be correlated with concomitant use of cocaine in heroin addicts.

Regarding substance abuse history, concomitant use of cocaine in heroin addicts correlated with patterns of heroin use (a history of failed treatments, the necessity to associate more than one treatment (methadone treatment and other psychoactive substances and/or psychotherapy and/or residential program), younger age of first substance use, younger age of continuous use and major dependence duration.

Table 3 shows the results of the backward logistic regression including as predictive factors those that proved to be significantly correlated with the concomitant use of cocaine in heroin addicts in the univariate analysis. On the basis of this analysis, the odds of having concomitant use of cocaine were higher for patients with double diagnosis (OR 1.37), especially for those affected with bipolar spectrum disorder (OR 1.39), and with psychotic disorders (OR 1.34), those with problems in romantic involvement (OR 1.36), and in legal problems (OR 1.41), and those who started continuous use younger (OR 0.98).

### Table 3

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds ratio</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD</td>
<td>1.37</td>
<td>1.21</td>
<td>1.53</td>
</tr>
<tr>
<td>“Bipolar spectrum”</td>
<td>1.39</td>
<td>1.15</td>
<td>1.63</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>1.34</td>
<td>1.14</td>
<td>1.54</td>
</tr>
<tr>
<td>Loving</td>
<td>1.32</td>
<td>0.18</td>
<td>1.46</td>
</tr>
<tr>
<td>Legal problems</td>
<td>1.41</td>
<td>1.31</td>
<td>1.51</td>
</tr>
<tr>
<td>Age of heroin continuous use</td>
<td>0.93</td>
<td>0.91</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Statistics: chi square 212.98, df 6, p<.001.

4. Discussion

4.1. Interpretation of results

Expectedly, cocaine using heroin addicts tend to show a greater level of work, legal and individual impairment (living alone and experiencing conflicts with significant others).

The younger age at first heroin use and younger age at continuous use is also expected due to the documented risk relationship between bipolar disorder and substance use. Wilens et al. (2004) identified juvenile-onset bipolar disorder as a risk disposition for adolescent drug use regardless of concurrent conduct disorder. Other authors (Rounsaville et al., 1991; Hahesy et al., 2002) concur that bipolar disorder typically develops after the onset of substance use, differently from conduct disorder, which tends to be a forerunner of substance use. However, it may be that some “minor” bipolar spectrum syndromes (featuring hypomania or temperamentel elation) running below the threshold of axis I disorders, or pictures meeting the clinical threshold as a consequence of episodic substance use, which have been referred to as bipolar III 1/2 (Akiskal and Pinto, 1999), typically precede the onset of sustained substance use (Camacho and Akiskal, 2005). Thereby, substance induced manic episodes and the chronic worsening effect of substance use may make subthreshold cyclothymic or hypomanic pictures to become full-blown bipolar disorders, sometimes with psychotic features (Winokur et al., 1998).

On the other hand, exposure to cocaine or other stimulants is not enough to elicit manic episodes, but requires an underlying bipolar diathesis, which can be revealed by the assessment of temperamental traits or accurate life-history for subthreshold cyclothymia (Silberman et al., 1981). Other authors have described the blocking effect of lithium upon amphetamine-induced euphoria, which was peculiar of subjects with a history of mood disorders (Van Kammen and Murphy, 1975; Silverstone et al., 1998). We therefore concur that the bipolar III 1/2 subtype (as well as the bipolar III, relating to antidepressants instead of drugs of abuse) is basically a variant of a bipolar diathesis, rather than mere bipolar-like expression of an intoxication from abused substances (Akiskal and Pinto, 1999; Camacho and Akiskal, 2005).

All in all, having a bipolar spectrum disorder would be a risk disposition to substance use (Maremmani et al., 2006) which, in its turn, would secondarily increase the rate of axis I bipolar disorder and of psychotic episodes.

The convergence of a bipolar diathesis and the involvement of stimulant use as means of a self-enhancement, and the resulting increase in severity and chronicity of
bipolar states, may be globally referred to as a bipolar-stimulant spectrum (Camacho and Akiskal, 2005).

The regression analysis in the present study revealed that cocaine using heroin dependent patients tend to have a higher rate of dual diagnosis: In fact, according to Skinstad and Swain (2001), cocaine abusers tend to have a higher rate of anxiety disorders in comparison with subjects who abuse just one substance. In particular, our data are consistent with the finding by Karam et al. (2002), who investigated the relationship between substance typology and psychiatric diagnosis in a sample of hospitalized abusers: Cocaine abuse was specifically related to a bipolar disorder dual diagnosis. The higher rate of concurrent treatments and failed treatments are predictable along the greater psychiatric complexity of such patients and the polyabuse status itself.

4.2. Limitations

The patterns of drug use in different communities may influence our results. In fact, in countries where cocaine is a second-line drug with respect of heroin, the bipolar-stimulant link may just mirror a higher level of bipolarity in this deviant subgroup. However, for subjects of such an age as our sample’s cocaine and heroin are equally likely to be first-line drugs. Also, the DAH-RS may have a limitation in distinguishing actual cocaine addiction from abuse and use: Therefore, some cases of past cocaine abuse or current controlled use may be omitted since self-rated as negligible, and the interviewer may focus on current or relevant periods of cocaine intoxication rather than generically on chronic exposure to cocaine. As a consequence, results may be limited to a relationship between current pathologic engagement into cocaine use and bipolar disorder. Obviously prospective data are needed to shed further light on the hypotheses derived from our clinical sample.

The sequence of events proposed from bipolar temperament, spectrum phenotypes, heroin and cocaine addiction, culminating in some cases to full-blown mania, even psychosis is plausible in light of the chronology of diagnoses as best we can reconstruct (see Section 2.2). The most crucial age at onset variable for our model is that for affective temperaments which, based on an Italian study is indeed in late childhood and early teenage years (Placidi et al., 1998).

4.3. Future perspectives

It is crucial in future studies to consider models where stimulant-abuse and temperament and/or personality can be viewed as sharing common genetic diatheses (Swend-}

sen et al., 2002). This plausible mechanism is beyond the scope of our essentially clinic-based strategy. Genetic epidemiology represents the optimum approach to test the latter perspective.

An animal model in which methamphetamine induces mania in small doses and eventually psychosis in higher doses has been described (Niculescu et al., 2000), and follows the well-known dopamine enhancing properties of this compound. In other words, in our model, stimulant “intoxication” is not the initial but the terminal event in the cascade of events depicted herein. The animal paradigm is beyond the scope of our more clinically-driven paper. The same is true for the experimental mechanism of sensitization in humans whereby repeated exposure to stimulants can enhance drug-induced psychomotor-responses and increased dopamine release (Boileau et al., 2006).

5. Concluding remarks

Cocaine use and polysubstance abuse among heroin addicts relates to a greater level of psychosocial burden and to the presence of dual diagnosis. Specific links emerge between psychotic syndromes and the bipolar spectrum. We submit that cocaine use plays the role of a pathophysiologic bridge between risk dispositions to substance use (subthreshold bipolar disorders) and their worsened or full-blown version (axis I bipolar disorders) as a consequence of recurrent acute or chronic stimulant intoxication. It has been hypothesized that cocaine abuse is an attempt to augment or optimize the level of baseline activation of one’s bipolar temperament. A more complex hypothesis would suggest heroin as an intermediary stage, i.e. an attempt to attenuate the constant or intermittent activation due to one’s level of cyclothymia and hyperthymia. The subject would then crave for more hypomania, leading to increasing cocaine use, abuse and eventually to full-blown bipolar disorder — even psychosis beyond mania.

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Conflict of interest
No conflict declared.

Acknowledgement

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

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