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# Comments on Lucire and Crotty, 2011

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## Dear editor

In a recent article, Yolande Lucire and Christopher Crotty presented their findings in an ongoing naturalistic study concerning a possible relationship between variant alleles in three CYP450 genes and a variety of behavioral problems.<sup>1</sup> Unfortunately, the tested population of 129 persons was very heterogeneous and poorly characterized from a phenomenological perspective. In the results section of their article, the authors use the term “akathisia” to describe the adversity, but without defining this phenomenon. They also use this term in the title of their paper. Since they state that the majority of the persons who experienced adverse clinical events had akathisia, which is not expected considering their clinical characteristics, it is possible that the term has been used to describe other types of problems rather than this well-defined extrapyramidal motor disorder.<sup>2,3</sup> In our opinion, this is unfortunate as it may lead to false interpretation of the mechanistic background of these putative side effects. As a matter of fact, such a false interpretation of the relationship between aggression and akathisia has probably led to misunderstandings during a number of court trials in the Netherlands. On one occasion, an accused person was sentenced to 24 years in prison because of an erroneous interpretation of the message of Lucire and Crotty’s paper.<sup>4</sup> Because the motor symptoms of akathisia were not confirmed by a small number of layman observers prior to his committing the felony, the judges rejected akathisia as a possible explanation for this aggressive behavior. It is important, therefore, not to use the term “akathisia” as being synonymous with drug-induced aggression. There are many other possible mechanisms which could cause selective serotonin reuptake inhibitors to lead to this type of adversity<sup>5</sup> and, in addition, it should be noted that adverse clinical events are only very rarely monocausally related to the intake of a drug.

## Disclosure

The authors report no conflicts of interest in this communication.

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## Author's reply

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## Dear editor

Lucire and Crotty<sup>1</sup> correlated the extrapyramidal side effect called akathisia with aggression, suicide, and homicide starting in the 1950s. Akathisia ranges in intensity from mild discomfort to the most painful and dangerous mental state known to psychiatry. Research from the pharmaceutical industry has also correlated antidepressants with akathisia suicide and diminished activity at CYP450.<sup>2</sup>

Along with intense dysphoria, the subjects, few of whom had a prior history of mental illness, suicidality or aggression, experienced variable and shifting combinations of neurotoxic phenomena: thoughts of death and dying, uncharacteristic aggression, suicidality, impulsivity, insomnia, paroniria, restless pacing (sometimes only at night), driving long distances in a dissociated state, exercising excessively to work off energy, worsening depression and/or manic shift along with behavioral dyscontrol. Each drug's product information lists some of the myriad manifestations of neurotoxicity which are also documented in the International Classification of Diseases (F10–F19: Mental and behavioral disorders due to psychoactive substance use), in *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV and in DSM-5 as a dozen substance/medication-induced disorders listed alongside the mental illnesses they suggest or mimic. Being side effects or intoxications and not mental illnesses, they have no numerical codes. DSM-III defined akathisia as a subjective desire to be in constant motion caused by drug sensitivity.

Inquiry must be made about how the subjects feels outside of the interview room, as this movement disorder fluctuates and is often missed, only treacherously to return an hour or a day later.<sup>3,4</sup> Reports of subjective or objective restlessness are strongly associated with aggression, violence, and suicide and can forewarn of a psychiatric emergency. Of the subjects tested in Lucire and Crotty, a handful could not sit still during the consultation and episodes of restlessness were many times more frequently reported than observed. The subject's mental state had more predictive value than

observed movements defined by the Barnes Akathisia Scale.<sup>5</sup> According to DSM-IV, the condition fluctuates and the subjects described bouts of restless legs, twitching, toe turning, pacing, and other activities occurring outside of the interview hours.

In clinical trials presented to the United States Food and Drug Administration for each drug's licensing, akathisia rates were underestimated because the condition was recorded only when its physical manifestations appeared in front of the interviewer. Because of this systemic error, resulting in the underdiagnosis of this condition, suicides occurred on active substance and in withdrawal in most clinical trials for antidepressants.

Professor Loonen's notion that identification of akathisia should be limited to what has been observed within a very circumscribed timeframe would result in even more cases being missed, with tragic consequences.<sup>6</sup>

The person to whom Professor Loonen refers to was prescribed paroxetine (Inh 1A2, Inh 2C9, Inh 2C19, Sub Inh 2D6, Inh 3A4) for marriage difficulties, and he took it irregularly.<sup>7</sup> On the day in question, he took 40 mg and, for his asthma, he inhaled an unknown quantity of budesonide (Sub 3A4) and formoterol (2A6, Sub 2C8, Sub 2C19, Sub 2D6) while he drank his habitual dozen beers. Alcohol inhibits CYP2B6, CYP2C9, CYP2C19, and CYP3A4.

He then suffered a psychological blow and, by his account, his "lights went out" and he suddenly became violent, fetched an antique gun, smashed a window, shot and injured two people, then he drove further and killed another person and continued to drive for several more hours while feeling both hot and cold and shaking violently. The court rejected evidence on the basis that akathisia was not observed before he developed it quite suddenly when he experienced a psychological blow. The sequence of events was poorly understood by the court. The homicidal behavior was concurrent with symptoms of serotonin toxicity which is associated with akathisia and manifested in his restless driving and aggression which were followed by patchy amnesia.

The only way that akathisia can be diagnosed after an event is by asking the patient about his mental state, experience, and behavior at the time of the homicide.

The appeal was not lost because of a judicial misinterpretation of Lucire and Crotty, but because Professors Loonen and Verkes were apparently unaware of the literature describing acute episodes of violence caused by an interaction between alcohol and selective serotonin reuptake inhibitors (SSRIs), so they attributed his homicidal behavior to alcohol, while telling the court that akathisia had not been observed by

others who saw him before it developed. Alcohol interferes, perhaps by competing, perhaps pharmacogenetically, with the metabolism of the SSRI, or the SSRI interferes with alcohol metabolism sometimes producing pathological intoxication and sometimes concurrent violence. Case reports show blood levels of alcohol to be much higher than expected from the volume consumed. Our opinion was that this man's habitual consumption of alcohol, together with a starting dose of 40 mg of paroxetine (with side effects which include impulsivity, akathisia, restlessness, and aggression) together with a psychological blow precipitated this episode of homicidal akathisia.<sup>8</sup>

Akathisia is rarely monocausal in clinical practice. It is dose related and cases formerly thought to be idiosyncratic are now known to be associated with diminished cytochrome metabolism, the co-prescription of cytochrome inhibitors, the removal of inducers, competition from polypharmacy for enzymatic substrate, diet and age of the patient, and their general and liver health.

## Disclosure

The author reports no conflicts of interest in this communication.

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