

# This Week's Citation Classic

**Crane G E.** Tardive dyskinesia in patients treated with major neuroleptics: a review of the literature. *Amer. J. Psychiat.* 124(Suppl.):40-8, 1968.

[Psychopharmacology Research Branch, National Institute of Mental Health, National Institutes of Health, Chevy Chase, MD]

Between 1957 and 1966, 34 papers were published on tardive dyskinesia, an irreversible side effect of neuroleptic drugs used for psychoses. The cited publication reviews the literature on this disorder and attempts to bring to the attention of the medical profession the hazards of the long-term prescription of these chemicals. [The Science Citation Index® (SCI®) and the Social Sciences Citation Index® (SSCI®) indicate that this paper has been cited in over 265 publications since 1968.]

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"Abnormal motility in patients receiving neuroleptic drugs had been reported since such agents were first introduced in psychiatry, but what most clinicians did not know was that motor disorder could be permanent and sometimes disabling. I became aware of this problem at a symposium in the Federal Republic of Germany in the winter of 1965 when Degkwitz<sup>1</sup> presented his observations on the condition later referred to as tardive dyskinesia. At that time, I was with the Psychopharmacology Research Branch of the National Institute of Mental Health (NIMH). I realized then that permanent damage of the central nervous system in drug-treated patients could become a major medical problem in view of the universal use of chemotherapy for psychoses. This was confirmed by a preliminary survey of patient populations I made in one of the hospitals collaborating with the NIMH and by studies I carried out throughout the 1970s.<sup>2</sup>

"The search of the literature for reports on tardive dyskinesia revealed that 34 papers had been published on this subject up to the end of 1966. While I was waiting for my investigations and those of others to be completed and published, I decided to devote a whole paper to a review of the literature. First, I wanted to give credit to all the authors who had made contributions in

this area. This would not have been possible if I had attempted to cover all the work done by previous investigators in the introductory portions of my original papers. Editors of scientific journals do not allow enough space for this purpose. Second, the number of contributions on tardive dyskinesia was very manageable. Thus, I was in a position to provide a complete review of the literature of an important medical problem. Ordinarily, this is an impossible task even in the most specialized area of biomedical research. Third, it seemed to me that the psychiatric profession should have been informed without delay of the hazards of prescribing powerful chemicals for long periods of time. In my preliminary survey and in subsequent examinations of hospital populations, I detected tardive dyskinesia in hundreds of persons, yet it was not diagnosed in a single case. Fourth, a complete and detailed report on the literature was important, because the topic was likely to be controversial due to the belief that neuroleptics were both effective and perfectly safe. In fact, the editor of the *American Journal of Psychiatry* made my manuscript available to N.S. Kline whose comments appeared as an addendum to my presentation in the same issue of the journal.<sup>3</sup> This unusual editorial procedure clearly indicates how important it was not to alarm the profession.

"The fear that psychiatrists would refrain from using neuroleptics for their patients proved unfounded. In fact, their prescribing habits have changed little over the years. On the other hand, clinicians in academia realized that tardive dyskinesia could have a major impact on the practice of drug use in psychiatry, which explains why the number of papers on this unsuspected complication increased exponentially in the 1970s. Significantly, most of the observations by the early investigators were confirmed by more sophisticated and generously funded research. Furthermore, basic scientists became aware of the possibility that a study of tardive dyskinesia could clarify some aspects of drug action on the brain. Thus, the cited paper contributed to research, which increased our knowledge of neurochemistry."

1. Degkwitz R, Wenzel W, Blussack K F, Herkert H & Luxenburger O. Zum Problem der terminalen extrapyramidalen Hyperkinesen an Hand von 1600 langfristig mit Neuroleptica Behandelten. *Arzneim-Forsch.—Drug Res.* 16:276-8, 1966.
2. Crane G E. Tardive dyskinesia and related neurologic disorders. (Iversen L L, Iversen S D & Snyder S H, eds.) *Handbook of psychopharmacology. Volume 10. Neuroleptics and schizophrenia.* New York: Plenum Press, 1978. p. 165-96.
3. Kline N S. On the rarity of irreversible oral dyskinesia following phenothiazines. *Amer. J. Psychiat.* 124(Suppl.):48-54, 1968.  
[The SCI indicates that this paper has been cited in over 45 publications since 1968.]