

# Mental Illness May Be Damaging to Your Brain

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**Issue:** *Episodes of psychosis, panic, mania, or depression may cause brain damage, which gives rise to disease progression.*

**N**eurons are the vessels that carry the cargo of mental illness through an electrical storm of symptoms. Recent evidence suggests that they may be damaged by the very process of ferrying angry, malfunctioning chemical and electrical events. As symptoms are shipped about the brain, they may leave behind weakened or sinking neurons due to the triggering of neuronal death by apoptosis<sup>1</sup> or necrosis<sup>2</sup> (see Figure). Some symptoms may be associated with the fading away of neurons by a quiet process of designer cell death called apoptosis.<sup>1,3,4</sup> Other symptoms may be associated with excitotoxic neuronal explosions due to chemical failure and, ultimately, messy necrosis.<sup>2,5-7</sup>

Shipwrecked neurons may explain why some mental illnesses such as panic, mania, psychosis, and even epilepsy have acute symptoms attributed to the brain being on fire, followed by

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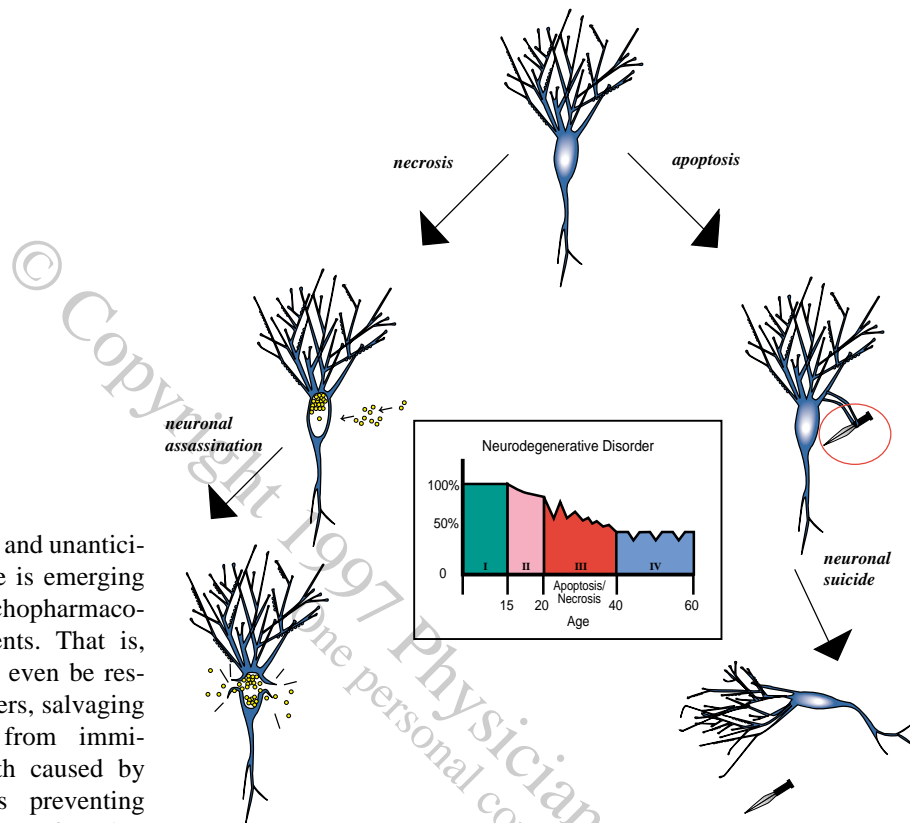
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## Take-Home Points

- ◆ Symptoms of mental illness may trigger apoptosis<sup>1</sup> and necrosis,<sup>2</sup> the neurobiological processes that hypothetically damage the brain
- ◆ Clinical consequences may be new acute episodes of mental illness, subsequent negative burnout symptoms, and diminishing treatment responsiveness
- ◆ Treatment may not only suppress acute symptoms of an ongoing episode of mental illness, but may also alter the natural history of the illness by interrupting destructive disease processes

the development of chronic empty symptoms attributed to burned-out neurons that are no longer able to mediate active symptoms or respond to treatment. Psychotropic drugs have long been recognized as firefighters, extinguishing the blaze of erupting symptoms of mental illness. More recently, they have been recognized to double as safety inspectors, in fact *preventing* outbursts of future episodes. For example, long-term maintenance with antidepressants, mood stabilizers, and antipsychotics provides prophylaxis against recurrent episodes of depression, panic, obsessive-compulsive disorder, mania, and psychosis.<sup>5</sup>

These concepts are shown in the figure, where a premorbid state (100% level of functioning, Phase I) is followed by an asymptomatic but prodromal state (Phase II). This in turn not only leads to chaotic symptoms of mental illness, which suddenly disrupt social and occupational function, but also triggers apoptosis or necrosis, which is destructive both to the brain and to the level of function in an ultimately progressive process (Phase III). Finally, a “burnout” stage (Phase IV) may emerge in which chaotic symptoms of mental illness are gone, but residual negative symptoms and treatment nonresponsiveness predominate.



A new and unanticipated role is emerging for psychopharmacologic agents. That is, they may even be rescue workers, salvaging neurons from imminent death caused by fire, thus preventing these neurons from being turned into ashes. By putting out the fire, coupled with preventing future outbreaks, these agents thereby prevent a cumulative destructive process (see Phase III in the Figure).

The rescue role is evident in the effects that the long-term administration of antidepressants and antipsychotics are having on disease progression. For example, the ability of antipsychotics to prevent future psychotic breaks appears to arrest the downhill course of schizophrenia.<sup>6</sup> Sufficiently clear evidence in this area has generated debate on whether conducting placebo-controlled trials in schizophrenia is ethical.<sup>6</sup> That is, those on placebo risk a relapse and possibly incremental brain destruction. Similarly, the “kindling” of future episodes of affective illness that are linked to reproductive events in women might be halted with antidepressant treatment.<sup>7</sup>

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Could prevention of symptoms of obsessive-compulsive disorder, panic, and social phobia similarly prevent the apparent treatment unresponsiveness of chronic uncontrolled anxiety disorders? Are these implications even more profound for the treatment of young patients with early-onset episodes of depression, mania, or psychosis? Is the flip side of early intervention that long-term suppression of symptoms will allow the brain to “heal” so that long-term treatment can eventually be discontinued? The child’s and adolescent’s brain may be more vulnerable than mature, possibly less plastic, brains to destructive ravages of the illness processes.

Answers to these questions promise to virtually revolutionize the use of psychotropic agents so that the treatment goals become complete elimination of ongoing symptoms,

complete prevention of future symptoms, and timely rescue of the brain from deterioration, even fostering healing and full recovery.

REFERENCES

1. Stahl SM. Apoptosis: neuronal death by design. *J Clin Psychiatry* 1997;58:183-184
2. Stahl SM. Excitotoxicity and neuroprotection. *J Clin Psychiatry* 1997;58:247-248
3. Koroshetz WJ, Moskowitz MA. Emerging treatments for stroke in humans. *Trends Pharmacol Sci* 1997;17:227-233
4. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry* 1995;52:998-1007
5. Stahl SM. *Essential Psychopharmacology*. New York, NY: Cambridge University Press; 1996
6. Carpenter WT, Schooler NR, Kane JM. The rationale and ethics of medication-free research in schizophrenia. *Arch Gen Psychiatry* 1997;54:401-411
7. Parry B. Reproductive related depressions in women: phenomena of hormonal kindling? In: Hamilton JA, Harberger PN, eds. *Postpartum Psychiatric Illness: A Picture Puzzle*. Philadelphia, Pa: University of Pennsylvania Press; 1992:200-218

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