Duration of untreated psychosis is defined as the time from an individual’s first psychotic symptom to the beginning of adequate treatment.1 In the United States, the median DUP is almost one and a half years, or approximately 74 weeks.2 This lengthy period of untreated psychosis can potentially have long-lasting health effects.

For decades, researchers have investigated whether long DUP has a toxic effect on neurological and psychological well-being and whether longer DUP is associated with worse social or treatment outcomes.

74 WEEKS is the average duration of untreated psychosis in the U.S.

This long period of untreated psychosis has many negative effects, including the following:
- Treatment response worsens.
- Insight is lower.
- Severity of symptoms increases.
- Neurotoxicity occurs in the brain.

Early detection and treatment can reduce these adverse effects and give individuals with psychosis a better chance at recovery.

**Structural brain health: Neurotoxicity**

Much of the research reporting on the effects of long DUP focuses on the correlation between DUP and neurotoxicity — examining the theory that prolonged or repeated episodes of psychosis leave scars on the brain that cause changes in brain structure, chemical compounds, or neuronal connections.3 For example, studies have found that long DUP is associated with the following negative effects:

- Temporal and occipitotemporal gray matter volume,4 which plays a significant role in daily functioning, physical movement, memory, and emotions,5 is reduced.
- Surface area in the salience and executive networks of the brain is reduced, and cortical thickness increases, all of which cause reduced functioning.6
- The brain registers higher levels of fatty acid amide hydrolase,7 which affects the brain’s ability to register feelings of pain and fear.8

Morphological changes in the brain may also be associated with the type of illness onset. For example, people with an insidious onset — meaning that the disease does not have obvious symptoms at first9 —may be more likely to have structural abnormalities due to long DUP.10
Neurotoxicity after first-episode psychosis
Although much of the research on DUP explores the potential for neurotoxicity during the first episode of psychosis, evidence suggests that untreated relapses of psychosis occurring after the initial clinical presentation of symptoms can also have a toxic effect on the brain. One study using structural MRI scans and cognitive testing found that long periods of relapse were significantly associated with tissue loss in the brain, including a decrease in total cerebral volume, frontal lobe white matter volume, and temporal lobe white matter volume. Researchers found that the duration of relapse impacted the extent of neurotoxicity, whereas the number of relapses did not.

How long DUP causes neurotoxicity
Two studies included in a 2014 literature review found that the neurotoxic effect of long DUP was caused by dopaminergic hyperactivity, or the prolonged elevation of dopamine, a naturally occurring chemical in the brain that is responsible for feelings of pleasure. Dopamine hyperactivity during a psychotic episode is thought to cause a progressive decline in the volume of certain brain structures. These studies suggest that neurotoxicity is caused by oxidative injury that arises from persistent neurotransmission activities, such as high dopamine and adrenaline levels during psychotic episodes. Similarly, another study argues that structural changes in the brain are caused by the inability to regulate dopamine release and prolonged overstimulation during psychotic episodes.

Social functioning and psychological outcomes
Research has shown that in addition to its adverse effects on structural brain health, long DUP can have a negative impact on social functioning and worsen psychosis symptoms. More specifically, studies have found that long DUP is associated with the following negative outcomes:

- The likelihood of comorbid substance use increases.
- Positive symptoms of psychosis, such as hallucinations and delusions, increase.
- Negative symptoms of psychosis, such as social withdrawal, increase.
- Insight is lower.
- Global functioning decreases (although this associated effect is considered to be relatively small).

A meta-analysis of data from 26 studies also found statistically significant correlations between long DUP (measured at 12 months) and all of the study’s measured outcomes, including the following:

- Depression/anxiety.
- Disorganized symptoms (which include incoherent speech patterns, difficulty performing daily activities, and inappropriate emotional response).
- Negative and positive symptoms of schizophrenia.
- Overall functioning.
- Quality of life.
- Social functioning.

Impact on treatment effectiveness
Research also shows that long DUP has a negative association with treatment effectiveness. One meta-analysis found long DUP to be a predictor of poor treatment response, and another study found that the longer the DUP, the worse the treatment response. Researchers suggest that this association is the consequence of the worsened brain...
network connectivity that results from long DUP.\textsuperscript{22} This research implies that earlier intervention might reduce the negative effect of long periods of untreated psychosis on brain health, thus leading to better treatment outcomes.

**Conflicting studies**

Not all researchers agree that long DUP has an impact on neurotoxicity or social functioning. A 2014 literature review concluded that there is limited evidence of a relationship between DUP and changes in brain structure or neurocognitive functioning; the researchers found that the majority of the studies observed in the review did not support the hypothesis that long DUP causes neurotoxicity.\textsuperscript{23} For example, a 2019 study from Switzerland found no significant relationship between DUP and changes in brain volume after adjusting for age and sex.\textsuperscript{24} With regard to social outcomes, a 2020 meta-analysis from the U.K. found that long DUP had no effect on employment, quality of life, or effectiveness of hospital treatment and concluded that any assumed association between long DUP and poor life and treatment outcomes might actually be the result of other factors, such as having good or bad coping mechanisms for psychosis symptoms.\textsuperscript{25}

However, some researchers have offered possible explanations as to why these studies do not find a clear association. For example, one group of researchers claimed that studies that have not found evidence of an association between long DUP and structural brain abnormalities tend to have small sample sizes or include patients who have already been exposed to antipsychotics, which skew results.\textsuperscript{26} Another group of researchers who found significant evidence that DUP is inversely correlated with brain function believe that commonly used methodological tools are not capable of accurately examining the effects of long DUP on the brain; these researchers suggest that newer methodologies, such as MRI scanners with stronger magnets and PET imaging, which many of the studies included in this summary used, are much better at capturing these brain processes.\textsuperscript{27}

**Benefits of early intervention**

The majority of relevant research displays convincing evidence that long DUP is correlated with adverse structural brain health and negative psychological and social outcomes. These findings support the case for early treatment intervention programs aimed at reducing the length of untreated psychosis and thereby its impact. Some researchers have found that early intervention has mild positive effects on long-term outcomes for people with schizophrenia. For example, one study with a 10-year follow-up period found that early detection of psychosis was associated with higher recovery rates and improved employment outcomes.\textsuperscript{28} Therefore, early detection and treatment interventions have the potential to reduce the adverse effects of long periods of untreated psychosis and give individuals with psychosis a better chance at recovery.
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