# Does the Onset of Efficacy for Agitation Vary Depending on the Administration Route of Antipsychotics?

**To the Editor:** Agitation is a common psychiatric emergency necessitating prompt management. A prevalence rate of agitation was reported to be 47.5% among 1,400 newly admitted patients with schizophrenia.[1] Antipsychotics are employed as the principal therapeutic strategy for acute agitation in psychosis.[2] In emergencies, antipsychotics are commonly administered via intravenous or intramuscular injection. An observational study showed that of 843 newly admitted agitated patients with schizophrenia, 45.5% received intramuscular antipsychotics within the initial 2 weeks of admission; 54.4% were administered oral antipsychotics exclusively, 39.9% were given both oral and intramuscular formulations, and 5.6% received only intramuscular antipsychotics.[3] A network meta-analysis of randomized controlled trials (RCTs) demonstrated superior efficacy of intramuscular ziprasidone, olanzapine, and aripiprazole at 2 hours and intramuscular olanzapine and aripiprazole at 24 hours post-administration over placebo or pseudoplacebo in agitated patients with schizophrenia.[4]

In clinical practice, injectable administration is usually expected to have a more rapid onset of action. Notably, injectable formulations exhibit faster absorption kinetics than their oral counterparts. For example, an RCT investigating the pharmacokinetics of aripiprazole—administered via intravenous, intramuscular, and oral routes—in both healthy subjects and patients with schizophrenia revealed faster absorption rates in intravenous and intramuscular formulations than that in an oral one.[5] Consequently, injectable formulations are postulated to have a more rapid onset of therapeutic effect than oral ones. Nonetheless, the majority of RCTs have primarily focused on the efficacy of antipsychotics for agitation based on their pharmacological types rather than their administration routes. In a review focusing on the efficacy of intramuscular versus oral antipsychotics, which encompasses 11 studies, only a single RCT directly compared the efficacy for agitation between different administration routes of the same antipsychotic.[6] Within this rater-blind RCT from 2010, 42 agitated patients with psychosis were randomized to receive either 10-mg intramuscular olanzapine, 10-mg oral disintegrating tablet (ODT) olanzapine, 3-mg oral solution risperidone, or 7.5-mg intramuscular haloperidol; 11 patients were allocated to the intramuscular olanzapine group, while 10 were assigned to the ODT olanzapine group.[7] The study found no significant differences in changes in the Positive and Negative Syndrome Scale—Excitement Component scores between the intramuscular and ODT olanzapine groups at every 15 minutes up to 120 minutes, 12 hours, and 24 hours. Given that this review was published in 2012, we performed an updated literature search on PubMed with the following keywords: (aggress* OR hostil* OR agitat* OR violen*) AND (antipsychotic* OR antipsychotic* OR neuroleptic*) AND (intramuscul* OR intraven* OR inhal* OR IM OR IV OR inject*), with a limitation of RCT. Surprisingly, our search yielded only the aforementioned study among 165 RCTs.

Due to the dearth of evidence, the question, "Does the onset of efficacy for agitation vary depending on the administration route of antipsychotics?" remains unresolved. As the choice of administration route is crucial during psychiatric emergencies, we strongly advocate for more RCTs that compare the onset of efficacy for agitation across different administration routes of the same antipsychotics (eg, oral vs short-acting intramuscular olanzapine and oral vs intravenous haloperidol).

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