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# Long-acting Injectable Antipsychotics during the COVID-19 pandemic in schizophrenia: An observational study in a real-world clinical setting

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## ABSTRACT

The COVID-19 pandemic is having an important impact on the practice of mental health services and on schizophrenia patients, and heterogeneous and conflicting findings are being reported on the reduction of long-acting injectable (LAI) antipsychotics use.

Aims of the study were to assess the total number of patients treated with LAI, the start of novel LAI and the discontinuation of LAI treatments, analyzing register data of the first year of the pandemic, 2020, compared to a pre-pandemic reference year, 2019.

Data from two outpatient centers were retrieved, for a total of 236 participants in 2020: no significant differences were observed comparing 2020 and 2019 when considering the total number of patients on LAI treatment ( $p = 0.890$ ) and the number of dropouts ( $p = 0.262$ ); however, a significant reduction in the start of LAI was observed ( $p = 0.022$ ). In 2020, second generation LAI were more prescribed than first generation LAI ( $p = 0.040$ ) while no difference was observed in 2019 ( $p = 0.191$ ).

These findings attest the efficacy of measures adopted in mental health services to face the consequences of COVID-19 and shed further light on the impact of the pandemic on the clinical practice of mental health services and on the continuity of care of people with schizophrenia.

## 1. Introduction

### 1.1. Background

The year 2020 marked the beginning of what has been defined by the World Health Organization as the greatest worldwide challenge that healthcare systems had to face in the modern era: the Sars-CoV-2 pandemic (Mahase, 2020).

Since the onset of the pandemic there have been, so far, more than 6 millions deaths and a total of almost 4 hundred millions of people infected worldwide (World Health Organization, 2022); Italy, and specifically the region of Lombardy, was heavily impacted by Sars-CoV-2 outbreaks in the first phases of the pandemic (Maruotti et al., 2022; Percudani et al., 2020).

People suffering from mental health disorders have faced a great hardship during the pandemic, especially when considering major

psychiatric diseases such as schizophrenia: recent literature highlights how people living with schizophrenia have an increased risk of contracting the virus and have a worse prognosis, considering both morbidity and mortality (Barlati et al., 2021; Kozloff et al., 2020; Mohan et al., 2021; Vita and Barlati, 2022).

Schizophrenia represents a debilitating psychiatric condition and although the severity of the disease is greatly variable the burden on patients' lives is usually high, leading schizophrenia to be classified among the top 10 global causes of disability (Freedman, 2003; Marder and Cannon, 2019; McCutcheon et al., 2020).

Schizophrenia is generally characterized by a variety of symptoms including positive, negative, and cognitive symptoms, with significant deficits in neurocognitive (Gold and Harvey, 1993; Nuechterlein et al., 2004; Vita et al., 2022) and sociocognitive performances (Freedman, 2003; Marder and Cannon, 2019; Pinkham, 2014). Such involvement of cognitive functions is strongly associated to a marked impairment in

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functional capacity (Mausbach et al., 2007), social skills (Patterson et al., 2001) and real-world functioning (Deste et al., 2020; Galderisi et al., 2018; Mucci et al., 2014).

The mainstem of the treatment of schizophrenia are antipsychotic medications (Keating et al., 2017), as they not only induce a reduction of symptoms but they can also achieve, when maintained for a sufficiently long amount of time and in association to other non-pharmacological interventions, a clinical and functional recovery (Vita and Barlati, 2018), with important repercussions not only on the patients' real-world outcomes, but also on their quality of life (DeRosse et al., 2018), global health and even mortality (Cullen et al., 2013; Liu et al., 2017).

However, such an achievement is a tough challenge, with patients often experiencing relapses, which entail a worsening of symptoms, cognitive performance and functioning that persist after the acute phase, compromising the establishment of a stable recovery (Novick et al., 2010; Robinson et al., 1999).

Pharmacological discontinuations is, therefore, a major issue throughout all the stages of the disease: the reasons for it are several, complex and often intermingled among them, involving all the three psychopathology domains (i.e. positive, negative and cognitive symptoms), the often scarce or superficial insight that is characteristic of the disorder, medication side effects, comorbid substance use disorder, therapeutic alliance and patient's health beliefs and environment (Lacro et al., 2002; Lieberman et al., 2005; Llorca, 2008).

Long-acting injectable (LAI) antipsychotic medications have been shown to improve adherence therefore increasing the odds of obtaining a stable recovery, leading to a reduction of healthcare costs of schizophrenia as well (Correll et al., 2016; Miyamoto and Wolfgang Fleischacker, 2017; Song et al., 2019). Long-acting formulations of the majority of the antipsychotic molecules commonly used in clinical practice are nowadays available and they are currently among the most effective treatments in psychiatry (Coutinho et al., 2000; Jann and Penzak, 2018; Madera et al., 2019; McDonnell et al., 2014; Subotnik et al., 2015; Tiihonen et al., 2017; Valsecchi et al., 2019). LAIs have also been shown to be effective on both core and non-core symptoms of schizophrenia, with a good tolerability profile (De Berardis et al., 2021, 2013) and are associated with a good level of patient treatment satisfaction (Fernández-Miranda et al., 2021).

Given the importance of LAI treatment for clinical stabilization and reduction of relapses in people living with schizophrenia, and the need for in-person visits to perform injects and deliver this specific treatment, the COVID-19 pandemic and the associated lockdowns created a worrisome situation where mental health services had to rapidly adapt to this new and unforeseen instance (Minelli et al., 2022; Moreno et al., 2020).

Many countries restricted access to healthcare structures for variable periods of time leading mental health centers to take different approaches to LAI prescription protocols: in some cases a switch from long-acting to oral formulations was preferred (Ifteni et al., 2020; MacLaurin et al., 2021; Shinn and Viron, 2020), whereas in some other instances no change was observed in the rates of LAI administration (Alevizopoulos and Nystazaki, 2021; McKee et al., 2021).

This new challenge regarding LAIs administration represented a cause of concern since the beginning of the pandemic. In fact, a study conducted in Romania and published as early as April 2020 reported that the restrictions caused by COVID-19 were associated to delays in pharmacies supplies, especially in rural and isolated area, resulting in a significant number of patients being switched to less expensive, easier to obtain, and more manageable oral antipsychotics; consequently, the number of LAI prescriptions fell by 49% for risperidone LAI and 90% for olanzapine LAI from December 2019 to March 2020 (Ifteni et al., 2020).

However, another study, conducted in USA and published only one month later, in May 2020, reported very different results: in fact, only a 10% reduction of LAIs' administration in the included mental health services; among the possible explanations of this finding, the Authors reported that their region was not a hot-spot for COVID-19, but also that

they quickly implemented their protocols to adapt to the pandemic (Gannon et al., 2020). Similar findings are reported in other studies, conducted in Greece and Canada (Alevizopoulos and Nystazaki, 2021; McKee et al., 2021).

Other works explored different aspects related to LAIs administration during the pandemic, highlighting the need to maintain an uninterrupted continuum of care based on protective protocols against the infection, close communication with community supports and careful planning with the patient is particularly important for stable clinical outcomes (MacLaurin et al., 2021; Nystazaki and Karanikola, 2021).

A recent healthcare provider-based survey reported that the administration and the prescriber-reported adherence to LAI antipsychotics remained substantially stable during the pandemic period in the USA (Zhdanova et al., 2022).

A consensus of experts and stakeholders from different healthcare fields participated in a round table discussion on the impact and challenges that the COVID-19 pandemics posed for individuals with schizophrenia and/or bipolar disorder: in particular, they stated that there was a decrease in the number of LAI prescriptions early on in the pandemics and they concluded that it was mainly driven by a decrease in the number of face-to-face consultations. They also discussed that, as highlighted by the pandemics, a fully integrated collaborative approach to ensure regular healthcare contacts and access to treatments is fundamental for the wellbeing of people living schizophrenia (Correll et al., 2022).

To stress the importance of LAIs in the treatment of schizophrenia, in September 2020, the American Psychiatric Association published a statement encouraging physicians to avoid the interruption of LAI treatments to high-risk patients, stressing the fact that this type of treatment is necessary for a favorable clinical course (Keepers et al., 2020).

However, literature regarding LAI treatments during the COVID-19 pandemic currently remains scarce and heterogeneous, and more information is needed regarding the impact of the pandemic on the use and prescription of LAI antipsychotics treatments the real-world, day-to-day clinical practice of mental health services, and specifically of mental health services of areas highly affected by the Sars-CoV-2 outbreaks.

## 1.2. Aims

The primary aim of the present study was to investigate how the COVID-19 pandemic impacted on the treatment of patients undertaking LAI antipsychotic medications, considering the total number of patients treated with LAI, the start of novel LAI prescriptions and the discontinuation of established LAI treatments in outpatient centers of mental health services, analyzing register data of the first year of the pandemic, 2020, compared to a pre-pandemic reference year, 2019.

The secondary aims of the study were to analyze the differences in the prescription of different molecules and/or group of molecules, such as first- (FGA) and second-generation antipsychotics (SGA), in the pandemic year 2020, compared to 2019.

## 2. MATERIALS and methods

### 2.1. Study design

This retrospective observational study was conducted analyzing register data for all patients accessing two outpatient services (I and III Mental Health Centers) of the Spedali Civili Hospital in Brescia, Italy, in the year 2020 and in the reference pre-pandemic year 2019. The two services have a combined catchment area of more than 250.000 individuals and in 2020 provided mental health care to 523 individuals diagnosed with schizophrenia. LAI prescription is provided by the treating psychiatrist on the basis of clinical assessment.

In each center, as routine clinical practice, a register is kept specifically for patients diagnosed with schizophrenia in LAI treatment. These

LAI-dedicated registers were accessed and screened to identify, for each included participant, sociodemographic variables and data regarding the molecules chosen for the treatment. Access to these registers, provided no data allowing identification of individual participants is disclosed, is allowed for research purposes as part of a larger network of studies regarding the treatment of Schizophrenia Spectrum Disorders (approved by the local Ethical Committee with the Project Identification Code NP 2902).

Inclusion criteria for the present study were: 1) diagnosis of Schizophrenia according to DSM 5 criteria; 2) treatment with a LAI antipsychotic; 3) age between 18 and 85 years old. Socio-demographic data were available only for the year 2020.

For the purpose of this study, the total number of patients treated with LAI in 2020 and 2019 was compared; patients the same comparison was performed analyzing the number of patients that started a LAI treatment in 2020 and in the pre-pandemic reference year 2019 and the number of patients who interrupted the LAI treatment in the same years.

The number of prescriptions that were made in 2020 and 2019 for each type of LAI molecule was also taken into account, and data from the two years was compared in order to identify possible changes in the clinicians' therapeutic choices. Molecules were considered both singularly and divided in categories such as FGA and SGA.

All LAI injections were administered in the clinic, which was left accessible for patients throughout the pandemic period with appropriate precautions to avoid contagion.

## 2.2. Statistical analyses

The  $X^2$  test and the Mann-Whitney test were used to compare sociodemographic variables regarding the patients of the two Mental Health Centers included in the present study. To account for both ethnical and cultural potential differences in a viable manner, nationality of participants was included in the analyses.

The  $X^2$  test was also used to compare the total number of patients treated with LAI in 2020 and 2019, the total number of patients starting LAI treatment in 2020 and in 2019 and the total number of patients discontinuing LAI treatment in 2020 and 2019.

A secondary analysis has been performed using the  $X^2$  test to compare the number of patients being treated with different types of LAI molecules (singularly and grouped as FGA and SGA) in 2020 and in 2019.

All the analysis were done using the IBM® SPSS® v.15.0 software. Values of  $p < 0.05$  were considered significant.

## 3. RESULTS

The clinical and sociodemographic characteristics of the enrolled patients for the year 2020 are as follows: a total of 236 patients were included, 155 males and 81 females. The age range varied from 21 to 84 years old, with a mean of  $51.44 \pm 13.33$  years. Two hundred (84.7%) participants were of Italian nationality, and 36 (15.3%) were of other nationalities. Of the total number of patients, 114 (48.3%) were selected from the I Mental Health Center, whereas 122 (51.7%) from the III Mental Health Center: there were no significant differences between the two Mental Health Centers regarding the number of LAI therapies administered ( $X^2 = 0.271$ ,  $p = 0.603$ ) and regarding patients' socio-demographic characteristics, in particular age (Mann-Whitney  $U = 6640.00$ ,  $p = 0.549$ ), sex ( $X^2 = 0.341$ ,  $p = 0.559$ ) and nationality ( $X^2 = 0.750$ ,  $p = 0.387$ ).

No significant differences were observed comparing pandemic year 2020 and pre-pandemic reference year 2019 when considering the total number of patients undertaking a LAI treatment ( $X^2 = 0.019$ ,  $p = 0.890$ ) and the number of dropouts ( $X^2 = 1.265$ ,  $p = 0.262$ ), whereas the number of patients who started a LAI therapy was significantly lower in 2020 if compared to 2019 ( $X^2 = 5.255$ ,  $p = 0.022$ ) (Table 1).

The secondary analyses performed to compare different molecules

**Table 1**

Comparison between 2020 and 2019 on primary outcomes.

Variable	Pandemic year 2020	Pre-pandemic reference year 2019	$\chi^2$ -test	p-value
Total number of patients treated with LAI	236	233	0.019	0.890
Patients starting LAI treatment	19	36	5.255	0.022*
Patients discontinuing LAI treatment	16	23	1.1256	0.262

LAI: Long-acting Injectable antipsychotic.

\* = p-value < 0.05.

between the two reference years didn't find any significant difference when the active principles were analyzed singularly. No significant difference could also be observed when grouping molecules in different classes, such as FGA and SGA (Table 2).

Finally, considering both years singularly, the comparison regarding the different classes of LAIs (i.e., FGAs and SGAs) between them showed that in 2019 there was no significant difference in the use of one group or the other ( $X^2 = 2.628$ ,  $p = 0.191$ ), whereas in 2020 SGAs were more used than FGAs ( $X^2 = 8.203$ ,  $p = 0.040$ ) (Table 3).

## 4. DISCUSSION

The COVID-19 pandemic still represents an important issue that mental health services are facing worldwide, particularly when considering the need to guarantee continued assistance to frail subjects in such a complex and delicate context (Moreno et al., 2020).

In people living with severe mental disorders, the isolation resulting from lockdowns and containment measures, combined with the risk of a reduction of availability of pharmacological treatments and psychosocial interventions, could lead to a significant worsening of their clinical condition, including a higher risk of relapse (Barlati et al., 2021; Hao et al., 2020; Thomas et al., 2020; Valdés-Florido et al., 2020; Vita and Barlati, 2022).

Considering the importance of LAI therapy in ensuring a stable treatment and avoiding relapses in people living with schizophrenia (Correll et al., 2016; Correll and Lauriello, 2020; Kishimoto et al., 2021), the present study aimed to assess whether and how the COVID-19 pandemic impacted on the continuity of care in users accessing outpatient services, considering also how it affected the starting of new LAI administrations and the discontinuation of previously established LAI treatments.

The recruited sample included a total of 236 (115 male gender and

**Table 2**

Comparison between 2020 and 2019 on secondary outcomes.

Molecule	Pandemic year 2020	Pre-pandemic reference year 2019	$\chi^2$ -test	p-value
Haloperidol decanoate	66	71	0.182	0.669
Zuclopenthixol decanoate	30	33	0.145	0.705
Risperidone	11	18	1.690	0.194
Aripiprazole	40	34	0.486	0.485
Paliperidone palmitate (3-4 weeks)	73	64	0.591	0.442
Paliperidone palmitate (10-12 weeks)	16	13	0.310	0.579
Total number of FGA-LAIs	96	104	0.320	0.572
Total number of SGA-LAIs	140	129	0.450	0.502

FGA: First-generation antipsychotic; LAI: Long-acting Injectable antipsychotic; SGA: Second-generation antipsychotic.

**Table 3**

Within-year comparison on antipsychotic categories.

Year	FGA-LAIs	SGA-LAIs	$\chi^2$ -test	p-value
2019	104	129	2.628	0.191
2020	96	140	8.203	0.040*

FGA: First-generation antipsychotic; LAI: Long-acting Injectable antipsychotic; SGA: Second-generation antipsychotic.

\* = p-value < 0.05.

81 female gender) participants diagnosed with schizophrenia, whose data were retrieved from the LAI registers of outpatient services: in this regard, the observed sample can be considered very representative of the investigated population, as data were gathered in a real-world mental health setting where day-to-day clinical assistance is provided to users. Mean age of participants was quite advanced (51 years), suggesting that the vast majority of participants was represented by individuals in chronic stages of the illness; however, several younger patients, with a lower duration of illness were also included in the analyses. No substantial differences emerged regarding participants recruited in each center, confirming the homogeneity and representativeness of the total sample.

The proportion of non-Italian participants in the study was 15.3%. Several studies show that COVID-19 pandemic increased pre-existing social and health-related inequities, and this is also true in the field of mental health (Gibson et al., 2021; Miconi et al., 2021; Reme et al., 2022; Sommer and DeLisi, 2022). There is also evidence that, in some contexts, LAI treatments are disproportionately used in patients of ethnic and cultural minorities: for instance, in the USA they are more used in Black patients than in White patients (Brown et al., 2014; Lawson et al., 2015). In the present study, the prevalence of non-Italian participants reflects the local population according to epidemiological data gathered in 2020, which reported a prevalence of non-Italian residents in the area that is only slightly lower, 12.4% (Istituto Nazionale di Statistica, 2020). This finding suggests that in this context no large-effect disproportion in the use of LAI treatments during the pandemic period could be observed, but more dedicated studies and scientific evidence is required on this relevant issue.

No significant difference emerged regarding the total number of patients treated with LAI in 2020 and in 2019. This represents a very interesting finding, especially in the light of the need to restrict the access to hospitals and health care facilities that has been necessary in the vast majority of countries worldwide during the COVID-19 pandemic and that, in some locations, combined also to supply issues, has led to frequent switches from LAI to oral formulation treatments (Ifteni et al., 2020; MacLaurin et al., 2021).

However, this result is in line with the recommendations issued by the American Psychiatric Association, which suggested to avoid discontinuation of LAI treatment, particularly in patients in chronic phases of the illness despite the difficulties presented by the pandemic (Keepers et al., 2020), and with the results of other recent studies conducted in the USA (Gannon et al., 2020; Zhdanova et al., 2022).

This objective was fulfilled, in the context explored in the present study, by frequently conducting clinical evaluations in teleconferencing, by screening with telephone interviews the presence of symptoms of COVID-19 infections in service users before home visits and by increasing the number of home visits compared to in-service visits. This allowed to lower the risk of contagion but also to guarantee continuity of service for users. Intervals between LAI injections were also increased in order to reduce the frequency of visits and the risk of contagion, opting for molecules with longer between-injections intervals where possible.

No significant difference was also found regarding the number of LAI treatment dropouts observed in 2020 compared to that observed in 2019. In this regard, the COVID-19 pandemic did not appear to have a consistent negative impact on discontinuation of LAI treatments. This is an interesting finding, particularly in light of the fact that the COVID-19

pandemic strongly accentuated the barriers to access mental health care for many patients (Moreno et al., 2020; Spagnolo et al., 2022; World Health Organization, 2020). As no increase in treatment dropouts were observed comparing pre-pandemic and pandemic period LAI treatments, it may well be that being on LAI helped to, at least in part, overcome these barriers. This could be due both to the better clinical stabilization that LAI treatment often provides, and to a greater clinical attention dedicated by clinicians to patients in LAI treatment (Correll et al., 2016; Correll and Lauriello, 2020).

Moreover, while no direct assessment of treatment satisfaction was performed for the present study, this finding suggests that patients' compliance to injections during the pandemic period did not decrease in a significant manner.

However, a significant difference was observed in the number of LAI treatments started in 2020 compared to 2019, highlighting a reduction of novel LAI administrations during the pandemic.

This might be due to several factors: the reduced number of in-person visits might have represented a deterrent to start a LAI treatment, and oral formulations may have been kept in some patients, particularly if they showed comorbid medical conditions that could lead to hospitalization in case of Sars-CoV-2 infection, fearing also potential issues of pharmacological interactions with medications administered in intensive care units without the possibility of suspending antipsychotic treatment.

Moreover, in patients with longstanding clinical stability, starting a LAI treatment could have led to an increase in the number of in-person visits, rather than a reduction.

Considering the trend in the use of specific molecules, no significant difference can be observed between 2020 and the pre-pandemic reference year. However, even if it does not reach statistical significance, a decrease in the number of patients treated with LAI Risperidone and an increase in the number of patients treated with LAI Paliperidone, both 1-monthly and 3-monthly: this result confirms the tendency to promote LAI treatments with longer between-injections intervals in order to minimize the need to meet in-person.

Regarding comparisons between FGA and SGA LAI treatments, no significant difference was observed in the use of each category of molecules comparing 2020 to 2019. However, comparing the number of patients treated with FGA and SGA within each year, no difference was observed in 2019, while a significant difference was observed in 2020, with SGA being preferred.

This finding suggests that, even during the pandemic period, a tendency toward using second-generation molecules instead of first-generation ones could be observed. This is in line with the most recent treatment recommendations, highlighting a favorable profile of SGA regarding safety and adverse effects (Leucht et al., 2017; Ohi et al., 2022), but also a better efficacy on negative and cognitive symptoms (Baldez et al., 2021; Galderisi et al., 2021).

Again, the shorter between-injections intervals of some first-generation molecules, such as Zuclopentixol, that requires 2-weekly administration, compared to the longer between-injections intervals of most second-generation molecules, could have played a role in this positive effect.

This study presents a series of strengths. Assessed data were directly gathered in real-world clinical setting, with a large catchment area and a large sample size and can be considered very representative of the explored context. The discussed findings also have considerable novelty, as there is a dearth of comprehensive assessments of the use of LAI antipsychotics in the first year of the COVID-19 pandemic, particularly in high-income areas that were also heavily affected by SARS-CoV-2 outbreaks. Moreover, this study was independently conducted, without any financial or commercial support from pharmaceutical companies that might represent a conflict of interest and a source of bias.

However, some limitations have to be taken into account. No assessment of the motivation that led to discontinuation of LAI treatment was conducted, which could have been highly informative on

various aspects of the impact of the COVID-19 pandemic. Moreover, no data regarding the clinical condition of included participants, including changes in symptoms severity, was available. No data regarding cognitive performance of participants, allowing to rule out potential cases of overlap of intellectual disability, was also available. These limitations, however, are intrinsic to the retrospective, register-based design of the study. Finally, no data regarding the use of LAI Olanzapine could be gathered and included in the present study, as this specific molecule was routinely administered in a hospital setting, in order to allow better monitoring of potential post-injection syndrome symptoms and not in the outpatient centers included in the study.

In conclusion, this study shows that no consistent reduction in the use of LAI antipsychotics was observed in an area heavily affected by Sars-CoV-2 outbreaks in the 2020 year, compared to the previous year; a decrease in the start of LAI treatments, however, occurred. These findings attest to the efficacy of measures adopted in mental health services to face the consequences of COVID-19 and shed further light on the impact of the pandemic on the clinical practice of mental health services and on the continuity of care of people living with schizophrenia spectrum disorders.

As the COVID-19 outbreaks had a dramatic impact not only on the lives of people diagnosed with schizophrenia but also on those of people living with other severe mental illnesses, such as bipolar disorders (Fornaro et al., 2021), future studies should also focus on reporting data on real-world use of LAI treatments in other clinical populations during the COVID-19 pandemic.

Further reports, ideally investigating also the opinions of participants and their clinical situations, conducted in areas with different economic conditions and that were in different ways impacted by Sars-CoV-2 outbreaks, perhaps also with different approaches adopted in mental health services to face the COVID-19 pandemic, are warranted in order to further the knowledge in the field.

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### CRedit authorship contribution statement

**Stefano Barlati:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. **Gabriele Nibbio:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Francesco Bianchi:** Data curation, Investigation. **Elena Butti Lemmi Gigli:** Investigation. **Irene Calzavara-Pinton:** Investigation. **Caterina Cerati:** Investigation. **Jacopo Fiori:** Investigation. **Jacopo Lisoni:** Investigation. **Giacomo Deste:** Data curation, Formal analysis, Supervision. **Antonio Vita:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing.

### Declaration of Competing Interest

The authors declare no conflict of interest in the design, execution, interpretation, or writing of the study.

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