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Professor Alessandro Zuddas' impact and legacy – The influential networking and human connection skills of a passionate scientist, clinical academic, and pioneer in child and adolescent psychopharmacology

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ABSTRACT

Professor Alessandro Zuddas, from the University of Cagliari (Italy), passed away prematurely in July 2022. As a prominent figure in child and adolescent neuropsychiatry, he substantially influenced the fields of neurodevelopmental disorders and neuropsychopharmacology both nationally and internationally. Professor Zuddas was a renowned expert in basic and clinical research in child and adolescent psychopharmacology, an enlightened and stimulating educator, and a mentor to many students, residents, and senior colleagues. With his enthusiasm and unique ability to network, he contributed enormously to trace a path in the field that we continue to follow. His name will remain in the textbooks and articles he authored. Here, as colleagues and friends who had the honor to work with him, we provide our personal views of Alessandro's impact and legacy, which go far beyond his publications.

Alessandro Zuddas was a Professor of Child and Adolescent Neuropsychiatry at the University of Cagliari (Italy) and the Head of the local Child and Adolescent Neuropsychiatry Service. Sadly, he passed away prematurely in July 2022. A psychopharmacologist by training, he then specialized as a child and adolescent neuropsychiatrist. His numerous scientific contributions continue to be foundational for our field. As colleagues who had the honor and pleasure of working with him, we were fortunate to witness his uniqueness, not only as a clinical academic and scientist, but also as a human being. In this article, we highlight Alessandro's impact and ongoing legacy, which continues to inspire our daily clinical and academic activities, and those of many others.

1. Italian child and adolescent neuropsychiatry: The revolution engendered by Alessandro

The most important revolutions start from below. As a resolute leader and original thinker, always looking for new knowledge and solutions, Alessandro contributed to profoundly change the discipline of child neuropsychiatry in Italy, forever transforming its methods and goals. Alessandro started this revolution in the 1980s, a historical moment when American child and adolescent psychiatrists were shifting the discipline towards a neurobiological and evidence-based framework. By contrast, in Italy, psychopathological issues in children and adolescents were mainly considered through psychodynamic and psychosocial lenses, with skepticism towards standardized diagnostic criteria and psychopharmacological treatment in children. For instance, until the 1990s, ADHD was considered by most in Italy to be an "*American invention*", and most Italian neuropsychiatrists did not conceptualize it as a valid syndrome. Therefore, one of the most important aspirations for Alessandro became to train and teach. He was firmly convinced that only by adequately training future professionals would the mental health care for children and young people be significantly improved. Teaching often took place through involvement in research activities, always dedicated to learning, discussion, in-depth analysis, and thoughtful criticism of the literature, but also to developing clinical care skills and supporting the welfare and training of students. Alessandro's skills as an educator

rapidly expanded his impact across Italy. He built solid bridges not only with many younger colleagues, who recognized him as a true Maestro, but also with a generation of already trained consultants who were fascinated by this enlightened and creative pioneer. His unique lessons enabled clinicians to effectively respond to their patients' needs. His students and mentees throughout Italy and beyond are now so numerous that they can no longer be counted. They follow his footsteps and contribute to the growth of the discipline as he had always wanted, carrying a legacy of which they can be extremely proud.

“When you read a scientific work, look for its weak points, its limits and try to go further, to do better. When someone offers you a new idea, accept it if it seems good to you, but not before having discussed it.”

In addition, Alessandro contributed to a profound renewal of the Italian child and adolescent neuropsychiatric discipline. Italy has a unique child neuropsychiatric training program that combines pediatric neurology, rehabilitation with child and adolescent psychiatry. Alessandro strenuously contributed to strengthen the rigor and evidence-base of the psychiatric domain, contributing to combating the stigma of mental illness.

True to his commitment and despite many obstacles he faced, Alessandro substantially contributed to establish the foundations of evidence-based clinical psychopharmacology for children and adolescents in Italy. By introducing many standardized tools in child and adolescent psychiatry, he strongly endorsed a structured approach for assessing psychiatric disorders in childhood – a highly innovative cultural approach for an Italian child and adolescent neuropsychiatrist at the time.

In these ways, Alessandro transformed the conceptualization of psychiatric disorders in childhood and adolescence in Italy. *“Psychiatric disorders are not disorders of the soul but of the brain,”* he repeated, explaining the role of the brain and its dysfunction in mental disorders. Perhaps even more

importantly, Alessandro inspired a patient-centered approach to care, always grounded in scientific evidence.

As noted, Alessandro was first a neuropharmacologist, which deeply affected him by imbuing an appreciation of the extraordinary power of the scientific method in addressing complex questions. Beginning in the mid-1980's, his collaborations with Irv Kopin, chief of the Section on Immunopharmacology at the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, in Bethesda, MD, USA and colleagues focused on the basic science of dopaminergic neurodevelopment (Corsini et al., 1987; Schinelli et al., 1988). By 1988, these collaborations were also occurring within the Department of Neuroscience, University of Cagliari, Italy (Corsini et al., 1988). There, Alessandro used state-of-the-art methods, such as applying the MPTP toxic metabolite 1-methyl-4-phenylpyridinium ion (MPP⁺) to study striatal dopaminergic neurotoxicity (Zuddas et al., 1989a; 1989b). His focus soon encompassed embryonic neural grafts to reverse dopaminergic lesions, with this work conducted at the Institute of Pharmacology, at the University of Pisa, Italy (Zuddas et al., 1990; Fiszman et al., 1991; Zuddas et al., 1991; Zuddas et al., 1992a). His work extended to non-human primates, again at the University of Pisa (Zuddas et al., 1992b). By the mid-1990s, his basic neuroscience work was firmly established at the Department of Neuroscience of the University of Cagliari (Zuddas et al., 1994; Zuddas et al., 2002), now part of the Division of Neuropsychiatry. Once embarked on his mission to reshape Italian Neuropsychiatry, Alessandro applied the same scientific rigor to clinical questions, naturally focusing on medications that modulate the dopaminergic systems, such as stimulants and neuroleptics.

2. The research on neurodevelopmental disorders, the enlightened vision

Coming from a strong school on the Dopaminergic system, when in the mid-90s Alessandro stepped in the field of child and adolescent psychiatry, he naturally focused on the range of symptoms and related conditions hypothesized to be differentially affected by dopaminergic functioning. This

included, on one end, positive and negative symptoms characteristic of schizophrenia and schizoaffective disorders; on the other end hyperactivity, impulsivity and inattention characteristic of ADHD, as well as other behavioral challenging symptoms observed across a range of neuropsychiatric conditions, including autism. Alessandro underscored the relevance of recognizing these symptoms in childhood and adolescence. He led some of the initial open trials assessing efficacy and tolerability of the second-generation antipsychotic for early onset schizophrenia (Zuddas et al, 1996) and challenging comorbid symptoms in autism (Zuddas et al 1996, and 2000). As detailed below, he took on the challenge of obtaining authorization from the Italian Public Minister of Health to safely administer methylphenidate to children with rigorously established diagnoses of ADHD and transformed the national understanding and care of ADHD in childhood. He went further; with his earlier career colleagues carried on empirical studies assessing the safety and benefits of methylphenidate in children with a diagnosis of autism and co-occurring ADHD symptoms (Di Martino et al, 2004). Although preliminary, the results of all these efforts have contributed to a growing international literature that had a long-term impact on clinical science (e.g., Zuddas et al., 2000), and informed the design of subsequent larger international controlled studies (e.g., RUPP 2005).

Despite progress, Alessandro recognized the remaining knowledge gaps in the field of biological psychiatry. He was acutely aware that a deeper understanding of the biological mechanisms underlying neuropsychiatric conditions is necessary to attain more precise and, eventually, individualized targets for interventions. Alessandro's fine understanding of neurotransmitters, their functioning and interactions, granted him the ability to approach child and adolescent psychopathology through a neuromolecular lens. One of the marks of great minds lies in the ability to integrate different approaches to solve complex problems. Alessandro was a great mind. He was fascinated by macroscale neuroscience and thus encouraged, directed, and supported his mentees interested in seeking expertise in non-invasive neuroimaging approaches to child neuropsychiatry.

The long-term vision was to establish a bridge between neuroscientific advancements at the molecular and macroscale functional domains. Although the promise for this vision holds on and the methods to reach such goals continue to rapidly advance, the path towards reaching those goals is still long. Unfortunately, Alessandro will not be able to directly contribute to the next steps, but his vision, courage, and energy continue to guide and support those of us walking along that path. This is our commitment to his legacy.

3. The contribution to the growth of knowledge in ADHD and developmental psychopharmacology in Italy: the work with Dr Gabriele Masi

Alessandro Zuddas first met Gabriele Masi in the early '90s when he was recently settled in Cagliari. This was the period of the dawn of psychopharmacology in Italy, and Gabriele Masi had written at that time a small book on child and adolescent psychopharmacology, quite unusual given the times. Having had Alessandro a pharmacological background, both in Italy and during his USA experience, they immediately shared this interest and approach. ADHD was at that time completely unknown in Italy, and/or considered “an American fiction”, so they decided to gradually spread the knowledge of this disorder and its treatment, through seminars and courses all across Italy, contributing to a gradual change of the panorama of Italian child and adolescent neuropsychiatry. At that time, Methylphenidate was not marketed yet in Italy, and only the hospitals of Cagliari and Pisa imported it, from outside Italy, with the authorization of the Italian Ministry of Health, for a small number of patients. In 2002, Alessandro, Maurizio Bonati (who worked in the “Mario Negri” Institute for Pharmacological Research in Milan), and Gabriele Masi organized a Consensus Conference in Cagliari, with the participation of the Academies for child and adolescent neuropsychiatry, adult psychiatry, pharmacology, pediatrics, psychology, and including parents of young ADHD patients, and institutional Agencies, such as the Agenzia Italiana del Farmaco and the Istituto Superiore di Sanità. The final consensus statements summarized the principles of definition, diagnosis and

treatment of ADHD. Soon after, Alessandro and Gabriele Masi wrote, for the Italian Academy of Child and Adolescent Neuropsychiatry, the first guidelines for the treatment of ADHD. These events led, in the following years, to the marketing of Methylphenidate and Atomoxetine for the pharmacological treatment of ADHD, and strongly affected the Italian approach to our discipline.

In this context, in 2001, the first edition of an intensive five-day course of Child and Adolescent Psychopharmacology was organized in the Scientific Institute Stella Maris in Pisa by Gabriele Masi, Alessandro Zuddas and Giulio Perugi, adult psychiatrist at the University of in Pisa, and attended by about a hundred of participants. Since that first edition, every year we have repeated this course, as an important occasion for sharing practical knowledge of the clinical and pharmacological management of mental disorders from childhood to adolescence and in the transition to adulthood, with thousands of participants throughout these last decades, and after 2022 without the fundamental contribution of Alessandro. Such shared activities, including hundreds of seminars and courses all over Italy, were only a part of the contribute that Alessandro gave to influence the course of our discipline in Italy, from a theoretical, methodological and practical point of view, along with a great emotional participation and respect.

4. The contribution to EUNETHYDIS

The European Network for Hyperkinetic Disorders (EUNETHYDIS) is a global network that aims to facilitate high quality science of ADHD and its wider societal impact through clinical and basic science research collaborations across Europe in the spirit of openness, trust and support. Alessandro developed his academic scientific career from the early beginnings in close collaboration with Eunethydis, for which he became one of the key members during more than two decades. Alessandro's unique contribution to the Eunethydis is outstanding. He served on the advisory board supporting Joe Sergeant, founder of Eunethydis who chaired the Network until 2014, and helped to develop the programs of the Network meetings. He stayed as a close friend and esteemed advisor of

the next chairman, Tobias Banaschewski, until he passed away. Between 2002 and in 2007 Alessandro organized as local host the famous 13th and 18th Eunethydis Network meetings in Cagliari including also wonderful insights into the rich local art, history and culture. Alessandro cultivated a passion for these topics with the same intensity and dedication he poured on his work. Not surprisingly they are still in vivid memories of many participants of those meetings. Within Eunethydis, Alessandro enthusiastically encouraged and supported the development of earlier career colleagues and inspired them as a role model, a mentor and a teacher.

Within the European ADHD Guidelines Group (EAGG), a part of EUNETHYDIS, which has the purpose to develop knowledge and recommendations to clinicians in order to help the latter to apply scientific knowledge to practice, Alessandro contributed his profound expertise on developmental psychopharmacology. For example, he had a major role in developing the European treatment guideline on long-acting medications (Banaschewski et al., 2006). He became the principal investigator in several research studies on developmental psychopathology and psychopharmacology, including several EU-funded projects, many developed through collaboration with the Eunethydis Network (Man et al., 2023; Santosh et al., 2023; Balia et al., 2021).

He was one of the editors of the Oxford Textbook of Attention Deficit Hyperactivity Disorder (Banaschewski et al., 2018) an authoritative, multidisciplinary textbook covering the etiology, pathophysiology, epidemiology, clinical presentation, comorbidity, clinical assessment, and clinical management of ADHD, to which many Eunethydis colleagues contributed. Within Eunethydis Alessandro will be remembered not just for his many scientific contributions in the field of psychopharmacology, but as one of the best and most supportive colleagues, an extraordinary, wonderful person of deep humanity.

5. The European funded projects and ENPREMA

Alessandro was passionate about psychopharmacology not only about ensuring that everyone across Europe had access to the best medications but that this access was supported by the strongest evidence. He was one of the first child and adolescent psychiatrists to recognize the importance of working closely with the regulators to push for equity for children and adolescents needing psychiatric medications in systems that traditionally favoured adults. To this end Alessandro worked tirelessly to develop relationships with members of the Paediatric Committee (PDCO) at the European Medicines Agency (EMA). He identified that while PDCO had a broad membership across paediatric medicine and surgery there was no mental health expertise within the group. While he was not able to change this directly, he played in making sure that, when the new European Paediatric Regulation was announced child and adolescent mental health was identified as a key area of interest. This has had a significant impact on the development and licensing of ADHD medications in Europe and beyond. For example, it was due to the Paediatric Regulation that it became mandatory to include quality of life and functional outcomes as a part of the development package for companies developing new ADHD medications and seeking marketing authorization in Europe.

Following the launch of the Paediatric Regulation the EMA announced their intention to develop a European network of existing national and European networks, investigators and centers with specific expertise in the performance of studies in the paediatric population. The EMA asked for expressions of interest from research networks to join the new group named European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). Alessandro and Dave Coghill took on the task of proposing EUNETHYDIS as a potential founding member. This was a huge but ultimately very rewarding task that required bringing together evidence of all the clinical trials and psychopharmacological research conducted jointly by EUNETHYDIS members. The resulting application really highlighted not only the depth of this work but also the breadth as well as some of the gaps and opportunities.

In early 2012 EUNETHYDIS were informed that they had been accepted as one of the founding category 1 networks within Enpr-EMA and were invited to attend the launch meeting in March of

that year. EUNETHYDIS was for many years the only mental health and neurology network to be represented within the category A members and to be a member of the Coordinating Group. Alessandro and Dave not only attended the annual face to face meetings but also contributed to several of the key working groups and helping to develop both the short and long-term strategy of the network. This allowed child and adolescent mental health, not just ADHD, to have a voice at the table in discussions around the development of scientific quality standards for paediatric psychopharmacology research. It also allowed us to develop a deeper understanding of the relationships between the key stakeholders in the field including those with lived experience, national competent authorities, the pharmaceutical industry, CROs and pharmacists. This has had a significant impact on paediatric psychopharmacology in Europe and allowed other key networks, such as the ECNP Child and Adolescent Network to build on this work and further advance paediatric psychopharmacology in Europe and beyond.

6. The contribution to the European College of Neuropsychopharmacology (ECNP) and the ECNP Venice school

The ECNP is an independent scientific association dedicated to support applied and translational neuroscience research and education in Europe. Within this institution, Alessandro was a major advocate of child and adolescent psychiatry by leading and expanding over the years a Network of excellence devoted to Child and Adolescent Neuropsychopharmacology. During his tenure, this Network expanded up to 30 members and succeeded in getting funding for a high number of European research projects, promoting educational sessions within the ECNP Congresses and collaboration with researchers outside the Child Psychiatry field. He also leveraged the impact of the Child and Adolescent Neuropsychopharmacology Network and managed it to be included alongside EUNETHYDIS as one of the networks of excellence represented within the European Network of Paediatric Research at the European Medicines Agency (Empr-EMA).

One of Alessandro's main commitments was to raising awareness of, and advocating for the need to address, the high unmet needs in Child Psychiatry treatments. He led an instrumental paper by the Child and Adolescent Neuropsychopharmacology Network on this subject that, among other outcomes, helped paving the way for enhancing early collaboration between industry and researchers by bringing researchers' expertise to the design of clinical trials (Persico et al., 2015). He had also a wide and integrative vision of the field and some of his efforts were directed towards promoting the adoption of transdiagnostic approaches in Child Psychiatry research and beyond. By means of his participation in European research initiatives such as the connect 4 children (c4c) project, he was pioneer in supporting the development of multi-stakeholder meetings in child psychiatry as a way of bringing together patients and families, regulators, industry and researchers to propose new ways to accelerate development of treatments for some of these unmet clinical needs. These ideas, that he shared and defended in multiple fora during his very active professional life, have contributed to some of the upcoming major changes we will hopefully see soon in the paediatric regulation field.

The impact of Alessandro's leadership has also been instrumental in the expansion of high-quality teaching to improve clinical practice and children and adolescent's health and wellbeing. One of his major contributions within the ECNP was the creation of the School in Child and Adolescent Neuropsychopharmacology and its consolidation as a unique international educational initiative in child psychiatry. The school was first held in 2012 in Venice and, although initially conceived to take place every 2 years, due to its high demand (that doubled or tripled the number of available seats) was soon set as a yearly course. Until its last edition in 2022, the Venice school brought together every year more than 50 child psychiatrists from virtually every European country that shared with the faculty a week of science and friendship in a unique environment. The impact of the school was particularly relevant for colleagues practicing in countries where access to mentorship and high-quality education in child psychiatry was more difficult, and helped not only to increase knowledge and confidence in applying it, but also to create a sense of community and collaboration within young European child and adolescent psychiatrists with different backgrounds that lasted beyond the

duration of the school and that led some of them to develop successful projects (e.g., Stevanovic 2019).

We have been very fortunate, the ECNP and ourselves, to have been able to count on Alessandro, his leadership, his vision, and his generosity during all these years. He was an exceptional mentor, but not only due to his wide knowledge and expertise, but, more importantly, due to his generosity and his ability to make others feel listened to and relevant, confident and acknowledged. The kind of leader and mentor not afraid of counting with smart disciples, but, on the opposite, striving to make them grow up to their full potential. In a world in which it is so common that structures are maintained by the establishment, his view on the need for cooperation, inclusiveness, meritocracy, and full and open vision should be remembered and expanded.

7. The current impact and legacy in Italy and internationally

After more than two years since his passing, Alessandro's memory and legacy are still very vivid and enduring. Nationally, the psychiatric section of the Italian Society of Child and Adolescent Neuropsychiatry (SINPIA), which Alessandro helped develop as Vice President, continues to thrive and draw new members, who are engaged in a variety of academic, clinical, and political activities, ranging from organizing meetings on cutting-edge topics to liaising with governmental agencies to improve psychotropic prescribing practices. Additionally, they are involved in developing national evidence-based guidelines and conducting surveys to gain insights into current practices and improve them further.

Although many child and adolescent neuropsychiatrists in Italy now feel confident in prescribing psychotropics to children, they also acknowledge the importance of continuously updating their knowledge to stay abreast of the latest evidence, influenced by Alessandro's legacy. In this regard, the successful series of monthly national webinars, originally implemented by Alessandro as Vice

President of SINPIA, continues to feature webinars on psychopharmacology dedicated to honoring his memory.

One of the major impacts of Alessandro's unique networking skills has been the creation and nurturing of vital links between Italian child neuropsychiatrists, particularly those focused on psychiatric issues, and international experts in the field. This has helped overcome parochial attitudes that can hinder progress. Currently, Italian child neuropsychiatrists, especially those working in neurodevelopmental disorders and their treatment, continue to benefit from ongoing exchanges with international colleagues. For instance, international colleagues are usually invited to meetings of SINPIA, including the joint conference between SINPIA and the Italian Society of Neuropsychopharmacology. These interactions pave the way for valuable research collaborations and foster the mobility of students, trainees, researchers, and clinicians between Italy and other countries. Notably, Alessandro's influence remains strong not only among professionals but also within key associations of people with lived experience that strive to promote appropriate care for children and young people with mental health conditions. These associations are vocal and resolute in advocating for evidence-based assessment procedures and treatments for children and young people, with many parents fervently stating, "*Professor Zuddas told me...*".

Internationally, we highlight here the initiative of the ECNP-Child and Adolescent Network to create the *Alessandro Zuddas Prize* to support the development of early career researchers in the field, acknowledging the significant impact of the Venice School established by Alessandro. We also highlight the *Alessandro Zuddas* sections and training days organized by Eunethydis and its working group EAGG, aimed at promoting the translation of findings from neuroscience and empirical research into improved daily clinical practice.

Beyond these factual events, we believe that Alessandro's greatest legacy is perhaps embodied in his reassuring and compassionate smile, along with his tenacity. This reminds us every day that despite adversities and resource constraints, we, as a network of professionals grounded in mutual respect, should always strive to achieve more to help our patients and their families.

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