


## CASE REPORT

# Human Appeasing Pheromone (HAP) influence on behavior and psychopathological residual symptoms of patients with complex psychiatric disorders

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## Introduction

Pheromones are volatile compounds released into the environment through body secretions and perceived by members of the same species, in which they trigger a behavioral or hormonal response, or modulate endocrine states and development [1]. Initially described in insects, subsequently they have been detected and investigated in mammals [2]. A specialized region of the olfactory system, the so-called vomeronasal organ (VNO) or Jacobson's organ, is considered to be responsible for pheromones detection.

Although anatomical evidence for a specialized pheromone system in humans is still matter of debate, a VNO is present in our species [3], and a putative pheromone receptor gene is expressed directly in the human olfactory mucosa [4]. It is generally agreed that apocrine glands in the axillae and pubic region represent the main sources of human pheromones [5]: the main ones are

### Key Clinical Message

This article is a case-report series showing the effectiveness of a three-month exposure to a synthetic analogue of Human Appeasing Pheromone as add-on strategy to psychopharmacological treatment on behavioral and residual symptoms of three patients suffering from severe psychiatric disorders with complex clinical pictures.

### Keywords

Autism spectrum disorders, bipolar disorders, Human Appeasing Pheromone, obsessive-compulsive symptoms, pheromones, psychiatric disorders, separation anxiety, social anxiety.

4,16-androstadien-3-one (AND) and estra-1,3,5 (10),16-tetraen-3-ol (EST) which structurally resemble sexual hormones [6]. The first experimental evidence supporting the involvement of pheromones in some human behaviors was that reporting the synchronization of the menstrual cycle amongst women living together [7], and the one showing that odorless compounds from women's armpits of women could influence menstrual cycle duration [8]. In the next decades, accumulating data suggested the possible role of androstadienone in emotions [3], giving the demonstration that accessory olfactory bulb sends its terminals to hypothalamus and related brain areas [2, 9].

More recently, increasing attention has been directed toward potential therapeutic applications in psychiatric symptoms/disorders of a different class of pheromones, the so-called appeasing pheromones (APs), which are secreted in the breast region shortly after delivery [10] and characterized by almost the same chemical structure in all mammals including humans [11, 12]. A core of

three methyl esters of C16 and C8 unsaturated acids (oleic acid, palmitic acid, and linoleic acid) is associated with a group of two to three compounds varying from one species to another. Because of their reassuring and appeasing effects on both young and adult animals, the synthetic analogues of these pheromones currently are largely used in animals for the treatment of behavioral disorders [13].

The AP products are available under the forms of sprays, collars, and electric diffusers (the same technology used for antimosquito products) that gained a great success in the treatment of behavioral and anxiety-related problems in dogs and cats, with no side or adverse effects [14, 15]. A human AP (HAP) has been isolated by from the Montgomery glands' secretions of maternal breast region after delivery [11].

This article summarizes a series of case reports showing the potentiality of HAP as add-on strategy to standard psychopharmacological treatments on behavioral and residual symptoms of three patients suffering from complex psychiatric disorders. The patients, who all signed an informed written consent, received a synthetic analogue of the native secretion of HAP for 3 months by means of an electric diffuser located in their houses and covering an area of 50–70 m<sup>2</sup>. Each diffuser refill lasted about 4 weeks. Each chemical compound identified in the native secretion was obtained from industrial chemistry procedures and then used to form the AP synthetic analogue. All the methyl esters used to prepare the product were obtained from plant oils or semisynthesis: No animal derivatives were used in this product. All the compounds of the pheromone are methyl esters of fatty acids that are well known as compounds of several food products and well identified as nontoxic products.

## Case #1

Patient #1 is a 40-year-old, unemployed single woman who lives with her parents. She has been suffering from bipolar disorder of type I (BDI), according to DSM-IV-TR criteria, since her adolescence, when she had suffered from a mixed episode with psychotic features (persecution and reference delusions, auditory hallucinations), psychomotor agitation, aggressiveness, and sleeplessness. Subsequently, she alternated mixed episodes with depressive phases (depressed mood, diminished interest and pleasure, loss of energy, feelings of worthlessness, indecisiveness, and crying), with just short symptom-free periods and with a consequent severe impairment in work and social functioning. She had been treated with mood stabilizers, typical and atypical antipsychotics, tricyclic (TCA) or selective serotonin reuptake inhibitor (SSRI) antidepressants, and benzodiazepines that had led to a

significant global improvement consisting in mood stabilization, absence of psychotic symptoms, no aggressiveness, and no sleep disturbances. In any case, as residual and invalidating symptoms, in particular marked separation anxiety toward her parents, insecurity, social anxiety and performance/social avoidance, and hoarding behavior, were still present, HAP was proposed to her as an add-on treatment. Her coadministered pharmacological drugs were the following: lithium 900 mg/die, clozapine 50 mg/die, paliperidone 6 mg/die, paroxetine 20 mg/die, and imipramine 50 mg/die. After her informed written consent was obtained, she was exposed to synthetic HAP analogue for 3 months and maintained on the same drugs for at least 1 month before and throughout the entire HAP exposure period. At baseline (T0) and at the end of each month (T1, T2, T3), she underwent a psychiatric examination and assessed by means of rating scales specific for her residual symptoms. In particular, she was asked to fill in the following scales: Adult Separation Anxiety Self-report Checklist (ASA-27; [16]), Liebowitz Social Phobia Scale (LSPS; [17]), and Obsessive-Compulsive Inventory – Revised (OCI-R; [18]). Moreover, in order to objectively evaluate her overall functioning, her caregivers (parents and sister) were asked to fill the questionnaire Life Skills Profile (LSP). After just 1 month of HPA exposure (T1), a significant improvement in residual symptoms was observed and described by the patient herself, with no adverse effects. Even her parents, who carefully reported their opinion on clinical changes at T1 in a written form, testified the overall clinical opinion.

The clinical improvement was confirmed by the LSPS score that decreased of about 29% from T0 to T3 (T0: 48, T1: 29, T2: 28, T3: 34), while the LSP score increased of about 47% from T0 to T2 and of about 28% from T0 to T3 (T0: 96, T1: 110, T2: 141, T3: 123). On the contrary, no substantial changes were recorded for ASA-27 (T0: 54, T1: 57, T2: 59, T3: 57) and OCI-R (T0: 56, T1: 51, T2: 54, T3: 57).

## Case #2

Patient # 2 is a 20-year-old man living with his parents, who has been suffering from an autism spectrum disorder (ASD) and marked intellectual disability with pervasive deficits in cognitive, motor, and communicative functioning. He is unable to complete even the most rudimentary aspects of self-care such as eating and toileting, firstly referred for psychiatric evaluation because of severe self-injurious behavior. When we met him and his mother for the first time, his hands were covered by hyperkeratotic lesions and bleeding wounds as a result of bites, his face and ears were full of scratches and lacerations due to blows and slaps, he could not remain alone in a room or

without physical contact with his mother, and during the visit, he continued to cry, scream, and slap himself in the face. He was treated for about 1 year with a combination of anticonvulsants (carbamazepine up to 1200 mg/die), antipsychotics (haloperidol up to 6 mg/die and chlorpromazine up to 300 mg/die), and benzodiazepines (clonazepam up to 4 mg/die), while obtaining only poor and transient results. A trial with clozapine was not tolerated because of blood dyscrasias. Therefore, after informing his parents and obtaining their informed written consent, the patient was exposed to synthetic HAP analogue for 3 months, while maintaining the same psychopharmacological regimen during the entire HAP exposure period. At baseline (T0) and at the end of each month (T1, T2, T3), he underwent a psychiatric examination and his mother was asked to complete the LSP questionnaire [19]. After 1 month, the HAP exposure provoked a significant reduction in self-injuring (no more bleeding wounds), although he continued to slap himself only occasionally, in separation anxiety (he was able to stay alone in his room with no need of physical contact), and in screaming and crying during medical evaluation. LSP score increased of about 55% from T0 to T1 and of about 49% from T0 to T3 (T0: 73, T1: 113, T2: 111, T3: 109). No adverse effects were reported.

### Case #3

Patient #3 is a 34-year-old, unemployed single woman living with her parents and one sister. She has been suffering from BDI, according to DSM-IV-TR criteria, since she was 18. The index episode was a mixed one with psychotic features (persecution and reference delusions), feelings of sadness, indecisiveness, crying, diminished interest and pleasure, racing thoughts, psychomotor agitation, and severe insomnia. Then, she experienced multiple recurrences with a similar clinical picture. Treatment with anticonvulsants and lithium resulted to be ineffective and poorly tolerated. During the last 3 years, she was successfully treated with clozapine (up to 50 mg/die) and citalopram (20 mg/die), and gradually obtained mood stabilization, with no psychotic symptoms or sleep disturbances. Unfortunately, she was still suffering from some residual symptoms, such as marked interpersonal sensitivity, suspiciousness and mistrust, obsessive ruminations, separation anxiety toward her relatives, avolition, and social withdrawal. The patient was informed of the possibility to be exposed to synthetic a HAP analogue for 3 months and provided her informed written consent to this strategy. At baseline (T0) and at the end of each month (T1, T2, T3), she underwent a psychiatric visit and filled in the following scales: ASA-27, LSPS, and OCI-R. The OCI-R score decreased of about 69% from

T0 to T3 (T0: 13, T1: 9, T2: 6, T3: 4) and that of ASA-27 of about 33% from T0 to T3 (T0: 21, T1: 25, T2: 20, T3: 14), with no side effect. No substantial changes were observed for LSPS one (T0: 91, T1: 91, T2: 81, T3: 81).

### Discussion

The case-report series reported herein provides preliminary observations on the potential effectiveness as add-on treatment of a three-month exposure to a HAP synthetic analogue in some psychiatric patients, two suffering from BDI and one of autism and self-injurious behavior. HPA exposure seemed to provoke a significant improvement of some residual psychopathological symptoms/dimensions such as social anxiety, obsessive-compulsive symptoms, separation anxiety, and behavioral disturbances. These symptoms were persistent despite psychopharmacological treatment had led to an overall improvement of the clinical picture. To minimize the confounding effect due to changes in drug regimens, the patients were maintained on the same treatment for at least 1 month before and during the entire HAP exposure period. The clinical improvement was recorded during the monthly psychiatric examinations, shown by changes in the rating scale scores, and even reported from patients and caregivers.

Our observations are in line with the results of other studies exploring the potential pheromones effects on psychiatric symptoms. A placebo-controlled study on 30 patients suffering from major depressive disorder demonstrated that an intranasally administered pherin (PH10), a neurosteroid that specifically engages peripheral chemoreceptors in the nasal passages, elicited a rapid antidepressant effect. In particular, it caused a significant Hamilton Rating Scale for Depression (HRSD; [20]) score reduction and a Self-rated Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ; [21]) score increase already from the first week of administration [22]. A very recent phase-two, multicenter, double-blind, placebo-controlled, single-dose study on 91 women with generalized social anxiety disorder showed that another pherin (PH94B – 3 $\beta$ -androsta-4,16-dien-3-ol) significantly decreased anxiety during both a public-speaking and social interaction challenges [23]. Such studies suggest that some pherins could represent novel, effective, and well-tolerated treatment options for a specific mood and anxiety disorders.

As far APs are concerned, in the last 20 years they were proven to be effective in animals in the control and prevention of acute and chronic stress, aggression, but also in the treatment of anxiety disorders such as separation anxiety, various sound phobias (fireworks and thunderstorms), neophobia in puppies, transport-related problems, and social stress [13, 14, 24–26]. On the contrary,

no human study on HAP effects on psychopathological symptoms is available. Extracts of the Montgomery glands' secretions were tested on 22 infants: No evidence of adverse effects was reported, while the smell of breast areolar secretions increased inspiratory activity and sucking reflex of infants, significantly more than other tested odorous stimuli [10]. Moreover, a HAP synthetic analogue was tested in a placebo-controlled study on a sample of 100 children aged between 18 and 36 months: During pediatric visits, the children treated with HAP showed a significant reduction of anxiety, less increase in heart rate, and less behavioral signs of discomfort compared to those treated with placebo [27]. Consequently, the present case-report series is the first clinical experience on HAP effects on psychiatric patients. In all our patients, HAP exposure with a concomitant psychopharmacological regimen was rapidly effective on social and separation anxiety, obsessive-compulsive symptoms, and self-injurious behavioral disturbances.

These preliminary observations would suggest that pheromones, and in particular HAP, may possibly represent putative, novel, and "natural" therapeutic opportunities to fulfill some unmet needs in the treatment of complex psychiatric disorders, given also the evidence that HAP exerts a local action without systemic absorption, appears to have rapid effects and an excellent safety profile.

Therefore, further studies are extremely needed to explore its preclinical activities on different CNS parameters, as well as large randomized placebo-controlled studies to clarify its potential therapeutic effectiveness on different psychiatric disorders and/or specific symptom clusters or psychopathological dimensions.

## Conflict of Interest

None declared.

## Authorship

AP, PP, DM, AV, and AC: planned the study. FM, AV, and AC: selected and assessed the patients. AP, AV, DM, FM, AC, and PP: analyzed the ensuing findings, wrote and revised together the manuscript.

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