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Routine treatment pathways in a cohort of patients with major depression and suicidality in Italy: the ARIANNA observational study

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ABSTRACT

Background: Major Depressive Disorder (MDD) with suicidal ideation, intent, or behavior is a psychiatric emergency with controversial care management. Our study describes the comprehensive treatment pathways of this population in Italian routine clinical practice.

Methods: ARIANNA [NCT 04463108] is an observational prospective and retrospective cohort study involving both primary data collection and secondary data extract. A total of 137 adult MDD patients with suicidality were enrolled from 24 Italian care sites and followed for 90 days. Other than the description of treatment patterns, the impact of treatment on depressive symptoms and suicidality, the burden on the patient's and caregiver's quality of life, healthcare resource utilization and costs were described.

Results: Of the 133 eligible patients, 68.4% were female, and the median age was 47. Approximately half of the study population had a current severe major depressive episode. Treatment strategies at the time of active suicidal ideation with intent definition/confirmation (t0) were heterogeneous, increasing in complexity during observation. According to the MADRS, patients with remission at t0+1 day were 2.6%, with the mean total score decreasing from 37.2 at t0 to 32.3.

Limitations: The study sites were not randomly selected.

Conclusions: To the best of our knowledge, this is the first cohort study that prospectively describes the characteristics of patients with MDD and suicide risk in Italy, and how they are treated in clinical practice. The study confirms this is a difficult-to-treat population. In addition, a lack of rapid, effective treatment for reducing depressive symptoms and suicidality is observed.

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1. Introduction

Major Depressive Disorder (MDD) is a psychiatric condition that is estimated to affect approximately 1.3 million (2.5%) patients in Italy [1], representing a major public health challenge and a considerable economic burden. Symptoms include low mood, which encompasses persistent feelings of sadness and hopelessness, anhedonia, recurring suicidal thoughts, impaired concentration, and sleep pattern changes [2,3]. Consequently, MDD causes diminished quality of life (QoL) and functional impairment, affecting work/school performance and relationships [3–5]. MDD has been further identified as an independent risk factor for comorbidities different from the psychiatric ones, that may further affect patients' health [6].

Also, depressive disorders significantly burden the patient's caregivers [7], who may experience psychological, physical, and financial distress that may impact their mental health [8,9]. MDD is associated with an increased risk of suicidality, especially in presence of psychiatric comorbidities or feelings such as hopelessness and lack of social support [8,10,11].

Compared to MDD patients without suicidality, those with suicidal ideation and intent experience more severe depressive symptoms and psychiatric comorbidities, a higher impact on everyday activities and a worse QoL, resulting in a higher healthcare resource utilization [4,12].

Treating this population may be very challenging since depressed, suicidal patients need an immediate intervention [13,14] and they may be less likely to respond to pharmacological treatment than MDD patients without suicidality [15,16].

Antidepressants are often used as first-line pharmacotherapy combined with other treatments [2,11,17,18]. However, reaching their optimal efficacy may take approximately 4–6 weeks. This lag in the onset of action may lead to negative consequences, especially in suicidal patients who would need a rapid improvement of their symptomatology. Other options may be anxiolytics, hypnotics, lithium, antiepileptics and psychotherapy. However, most of these approaches are not effective in the short term or they are used despite limited scientific evidence. On the other hand, the use of electroconvulsive treatment is quite limited in routine clinical practice in Italy, even if its efficacy is well-documented in literature [11,19].

Patients with suicidal ideation often require hospitalization, however this is only a transient measure and there is a significant risk of relapse weeks after discharge [18].

To date, exhaustive data regarding both the standard of care and the real-world outcomes of MDD patients with suicidal risk in Italy are unavailable [20]. Furthermore, this population is often neglected in clinical trials per protocol or through selection bias [21], therefore data collection from the routine clinical practice by an observational study design has a high scientific value.

Moreover, it would be useful to explore healthcare resource utilization (HRU) and costs for MDD patients with suicidality in the Italian National Healthcare System context.

This study is descriptive, designed to observe and report data regarding subjects with MDD and suicidality in a specific time frame. For this reason, no formal hypothesis was pre-specified. The main purpose of this study is to generate real-world evidence, describing the clinical and demographic characteristics of this understudied population, the treatment utilization pathways and clinical and psychosocial outcomes over time.

Secondly, based on the sub-study protocol design, the study aims to capture relevant HRU and the associated costs for a subgroup of patients through administrative data retrieved from their Italian Local Healthcare Unit (LHU) databases (when accessible) and prospective data collected at centers. The analysis of these data should be valuable for estimating the economic burden for this condition.

2. Materials and methods

2.1. Study design and participant identification

ARIANNA [ClinicalTrials.gov Identifier: NCT04463108] was an Italian multicenter, observational, prospective, and retrospective cohort study. It can also be classified as a hybrid study: the main study collected primary prospective data, combined with the patient-, clinician-, and caregiver-reported outcome measures (assessed using validated questionnaires and scales), while the sub-study collected secondary retrospective data (Fig. 1A).

The ARIANNA study was conducted at 24 clinical sites in Italy, and data were collected from August 2020 to November 2021. Eligible patients for ARIANNA were adults, aged from 18 to 74, of both sexes, with a moderate to severe major depressive episode (MDE) – according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) – and concomitant active suicidal ideation with intent, based on clinical judgment. The core aspects for suicidality assessment, further inclusion and exclusion criteria, are described in the Supplementary Material. Subject were excluded if they had participated in or were currently enrolled in any clinical trial with experimental treatments within the current major MDE. Patients eligible for enrollment in the study were consecutively included in each site.

Caregivers of enrolled patients could participate in the study if they were 18 years of age or older.

All participants received a comprehensive explanation of the study procedures and goals, consistent with the Declaration of Helsinki, and all patients and caregivers voluntarily participated in this study after signing a written informed consent form. The study was approved by the local Ethic Committees of all participating institutions before the start of data collection (first approval of the Coordinating Ethics Committee on December 5, 2019; Prot. n. 274 SA_2019), and conducted following the guidelines for Good Pharmacoepidemiology Practices (GPP) [22] and applicable regulatory requirements.

2.2. Study evaluations

2.2.1. Procedures

Study observation started on the day when active suicidal ideation with intent was defined or confirmed (t0) by the Investigator in MDD-diagnosed patients.

Data were prospectively collected at enrollment (visit 1) and subsequent visits up to 90 days according to the current clinical practice (Fig. 1B).

Primary data collection continued until the end of observation (study visit 5). The observation could also end according to exit criteria reported in the Supplementary Material.

Patients identified in LHU Claims databases and included in the retrospective data analysis were observed in the three years before enrollment.

2.2.2. Primary objective

The primary objective of this study was to describe both the socio-demographic/clinical characteristics and the pharmacological/non-pharmacological treatment utilization pathways in patients with MDD and active suicidal ideation with intent in routine clinical practice. This analysis included the description of the comprehensive (pharmacological and care setting) treatment received by the patient for the current MDE (Supplementary Material).

2.2.3. Secondary objectives

Secondary objectives included a description of the impact of treatment pathways on clinical outcomes of depression and on the patient's QoL measured by patient-reported outcomes.

At each follow-up visit, depressive symptoms were measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) [23].

According to the MADRS, remission was defined as achieving a MADRS total score ≤10, while response was defined as achieving ≥50% improvement from baseline (t0) to the defined time-point in the MADRS total score. In addition, patient health status and QoL were assessed using the EuroQoL 5-Dimension, 5-levels (EQ-5D-5L) instrument, which included the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS), both primarily designed for self-completion by respondents [23]. All the tools used to characterize outcomes are described in the Supplementary Material.

The description of the safety and tolerability profile of current treatment pathways used was based on all adverse events (AEs) documented during the prospective observation, regardless of severity, or causality, for all eligible patients.

2.2.4. Exploratory objectives

As an additional exploratory objective, the ARIANNA study described the impact of treatment pathways on suicidality dimension, measured through clinician- and patient-reported outcomes. For this purpose, the Columbia-Suicide Severity Rating Scale (C-SSRS) [24–26] and the self-reported Beck Hopelessness Scale (BHS) [27] were recorded

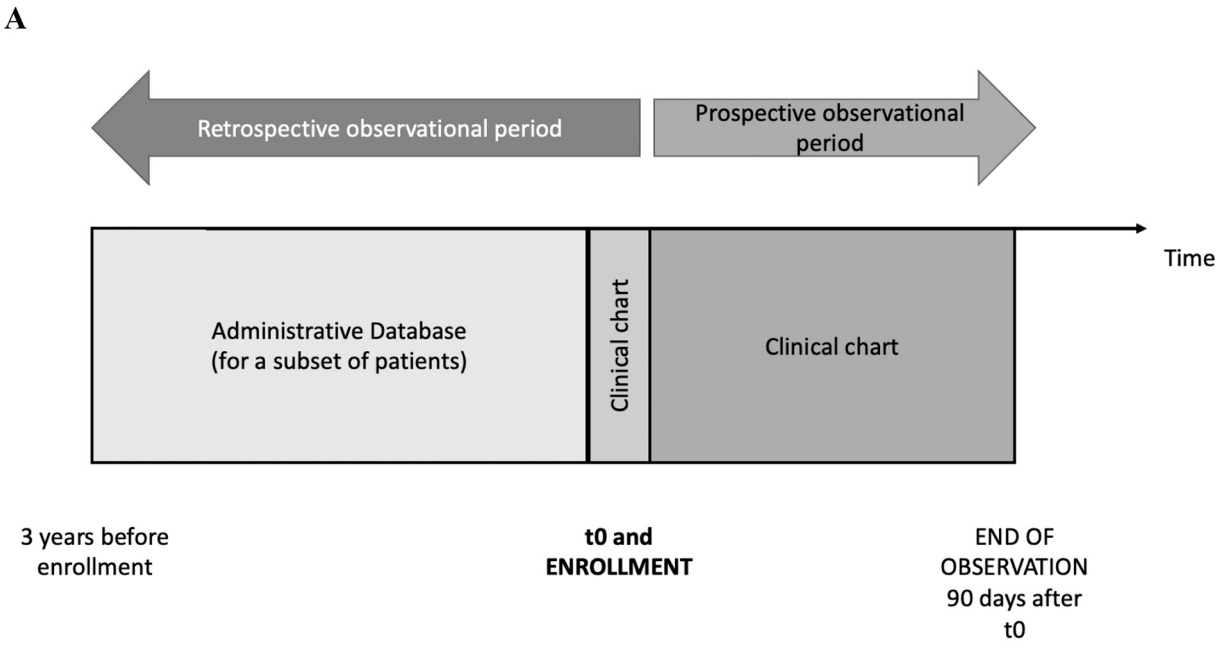


Fig. 1. Study scheme for the ARIANNA study: A) overall study scheme including the retrospective and prospective observation periods of ARIANNA; B) scheme for the prospective data collection.

Data were prospectively collected at enrollment (visit 1) and on expected visits according to the current clinical practice in Italy: 1 day after t0 (visit 2), at the end of hospitalization (or up to 2 days before), if any (visit 3), 30 (±7) days after t0 (visit 4). The last follow-up visit was expected 90 (±14) days after t0 (visit 5). Additional data were collected in the event of unscheduled visits or any significant clinical change (e.g., hospital admission/discharge, safety issues).

Caregivers could give their informed consent for participation either during visit 1 or visit 2.

t0 = day on which the 'active suicidal ideation with intent' condition was defined/confirmed by the Investigator. Visit 1 should correspond to t0, when possible.

during the observation period, and change over time was analyzed. The C-SSRS allows to assess behaviors which may be indicative of intent to complete suicide; the BHS is a patient-reported instrument that evaluates the level of negative expectation regarding the future, and it is an important predictor of future suicide. Furthermore, change in the MADRS item-10 on suicidality thoughts (MADRS suicidality item, MADRS-SI) was also taken into consideration.

The scores for the European version of the Involvement Evaluation Questionnaire (IEQ) [28] and their changes over time were also used to describe the impact of disease and treatment pathways on caregiver burden and distress.

The Supplementary Material describes the questionnaires and scales used to characterize clinician-, caregiver- and patient-reported outcomes.

2.2.5. Objectives of the sub-study

HRU and costs were estimated using medical records, combined with administrative data of LHUs for a subsample of patients. In the five investigating sites that approved the sub-study protocol design, primary data collected from the main study were deterministically linked at a patient level with data extracted from the corresponding LHUs to assess retrospective and prospective HRU and costs. The ARIANNA sub-study used administrative records available at the LHUs up to 3 years before enrollment for each patient (Fig. 1A) containing information on drugs used for psychiatric disorders; hospitalizations for psychiatric disorders; psychiatric or neurological specialist visits; laboratory tests, instrumental and other diagnostic tests related to the psychiatric disorder. To calculate costs regarding resource consumption at the patient level, each LHU provided the actual cost reimbursed for every resource recorded in the database. On the other hand, prospective data collected information on emergency department (ED) access/in-patient hospitalization, specialist out-patient visits and in-patient/day hospital access, prescription of laboratory tests, and instrumental and other diagnostic tests up to 90 days after enrollment. For primary data, costs were estimated both for the sub-study and the main study population using standardized references at the Italian level for each resource recorded [29,30].

2.3. Statistical analysis

Descriptive analyses were composed of mean (standard deviation, SD), median (25th Percentile-75th Percentile, 25th P-75th P), and absolute and relative frequencies, according to the considered variables. No formal statistical hypotheses were set for this analysis.

Statistical analyses were performed for all evaluable patients who had entered the study with available data. The analyses were performed using SAS Enterprise Guide v. 7.12 and SAS 9.4 (SAS Institute, Cary, NC, USA).

3. Results

Of the 137 patients enrolled in the main study, 133 (97.1%) were considered eligible and evaluable for the prospective analyses (Full Analysis Set, FAS; main study). Reasons for the exclusion of 4 patients were reported in the Supplementary Material. A total of 41 (30.8%) patients were enrolled in the sub-study and considered for the administrative data analysis.

Overall, 18 caregivers consented to the study and were considered eligible for the analyses.

3.1. Demographic and baseline characteristics

Among the 133 patients, 100 (75.2%) completed the study observation, while 33 (24.8%) prematurely withdrew from the study, mainly because of a loss to follow-up.

Of the eligible patients, 68.4% were female, and median (25th P-75th P) age was 47.0 (29.0–56.0) years (Table 1). The median (25th P-75th P) age at onset of MDD was 30.8 (22.8–46.3) years, with a median (25th P-75th P) duration of a current MDE of 1.2 (0.2–2.8) months from onset to t0 (Table 1).

Table 1
Socio-demographics and clinical characteristics of patients eligible for the ARIANNA study.

	Full Analysis Set (*N* = 133)
Age at enrollment (years)	
Median (25th–75th percentiles)	47.0 (29.0–56.0)
Sex, *n* (%)	
Male	42 (31.6)
Female	91 (68.4)
Highest level of education achieved, *n* (%)	
Less than primary school	3 (2.3)
Primary school or similar	3 (2.3)
Middle school/Secondary school (I level)	43 (32.3)
High school/Secondary school (II level)	58 (43.6)
Academic degree or higher	23 (17.3)
UNK	3 (2.3)
Current employment status, *n* (%)	
Unemployed/Not working	34 (25.6)
Retired/Leave of absence	13 (9.8)
Housewife	10 (7.5)
Student	19 (14.3)
Employed part time (<40 h/week)	7 (5.3)
Employed full time (40 h/week)	48 (36.1)
UNK	2 (1.5)
Current living arrangement, *n* (%)	
Cohabiting (with spouse/partner/parents/ friends)	110 (82.7)
Assisted living	1 (0.8)
Living alone	21 (15.8)
UNK	1 (0.8)
Personal history of psychiatric disorders, other than MDD (overall), *n* (%)	
No	98 (73.7)
Yes	34 (25.6)
UNK	1 (0.8)
Age at onset of MDD (years)	
N	133
Median (25th–75th percentiles)	30.8 (22.8–46.3)
Range	8.0–74.0
History of suicidal behavior before t0, *n* (%)	
No	90 (67.7)
Yes	43 (32.3)
Duration of current MDE from onset to t0 (months)	
N	133
Median (25th–75th percentiles)	1.2 (0.2–2.8)
Range	0.0–75.4
Type of MDE at t0, *n* (%)	
First depressive episode	25 (28.4)
Recurrent depressive episode	63 (71.6)
UNK	45
Severity of the current MDE, as per clinical judgment, *n* (%)	
Moderate	70 (52.6)
Severe	63 (47.4)
Current TRD episode, *n* (%)	
No	128 (96.2)
Yes	5 (3.8)

Abbreviations: MDD, Major Depressive Disorder; MDE, major depressive episode; TRD, treatment-resistant depression; h, hours; UNK, unknown.
t0 = day on which the 'active suicidal ideation with intent' condition was defined/confirmed by the Investigator.

The mean (SD) MADRS total score at t0 was 37.2 (7.4), and approximately half of the study population had a current severe MDE (*n* = 63, 47.4%), as per clinical judgment. On the other hand, only 3.8% of the patients had a current treatment-resistant depression (TRD) episode. The overall characteristics of the sample are summarized in Table 1 and in the Supplementary Material.

The experience of any past personal life events was described in 61 (53.5%) patients. Among the most reported events, marital separation/divorce was reported by 17 (27.9%) subjects, while 15 (24.6%) patients

reported the death of a close family member or a friend (Supplementary Material).

Psychiatric comorbidities were reported by almost 26% of patients, mainly anxiety. Approximately 30% of patients reported one (n = 18, 13.5%) or more (n = 25, 18.8%) prior suicidal behaviors.

Comorbidities other than psychiatric disorders were present in 49 (36.8%) patients, particularly hypertension (n = 14, 10.5%).

The median (25th P-75th P) age of the caregivers was 53.5 (43.0–66.0), and 10 (55.6%) were female. Caregivers were mostly mothers or fathers (38.9% and 33.3%, respectively), a spouse, a partner, or a person in a relationship with the patient (33.3%). Overall, 66.7% of caregivers cohabitated with the patients.

3.2. Comprehensive treatment pattern

Antidepressants were the first-line treatment (introduced or confirmed) at t0 for 104 (78.8%) patients out of 132 with available data. This proportion increased during the entire period of observation to up to 82.4% (98 out of 119 patients) at the end of observation. Before t0, 65.0% of patients (with available data) were treated with antidepressants. Anxiolytic drugs/hypnotics, antipsychotics, mood stabilizers/lithium or other kinds of treatments, were also prescribed for patients, and their use increased in frequency over time (Table 2). At t0, 27.3% (36 out of 132) of patients were treated with lithium, while antipsychotics were indicated in 68.2% (90 out of 132) of patients.

The most frequently prescribed antidepressants at t0 were selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs): sertraline (n/N = 28/132, 21.2%), venlafaxine (n/N = 16/132, 12.1%), paroxetine (n/N = 12/132, 9.1%), and citalopram (n/N = 11/132, 8.3%). Benzodiazepines were the most frequently used sedative/anxiolytic treatments. Details of the first treatment indication at t0, among antidepressant and non-antidepressant medications, are reported in the Supplementary Material.

In addition to polypharmacotherapy, 16.7% of patients at t0 also received psychosocial therapy. At the end of the observation, this percentage increased up to 19.3% (Table 2).

A meaningful change in treatment strategy between the week before t0 and after t0 occurred in 36.2% (n/N = 42/116) of patients with available data. At t0, antidepressant augmentation with mood stabilizers and/or antipsychotic drugs and optimization was the most frequent approach observed in 80 (60.6%) and 31 (23.5%) patients out of 132, respectively. A summary of pharmacological treatment strategies in the week before t0 and at t0 is indicated in Fig. 2.

Between 31 days after t0 and end of observation, 100% of evaluable patients (N = 119) were still on pharmacotherapy, and polypsychopharmacological approach was mostly considered (n/N = 103/119, 86.6%). Augmentation was the most frequent management strategy chosen, followed by antidepressants combination (77.6% and 32.7%, respectively).

3.3. Depressive symptoms

There was a slight but progressive decrease of the MADRS mean (SD) total score during the observation period: from 37.2 (7.4) at t0, to 32.3 (9.4) at t0+1 day, to 14.0 (8.6) at the end of hospitalization (after a mean [SD] duration period of 11.0 (6.6) days from t0), and to 12.6 (9.3) at t0+90 days for the evaluable patients (Fig. 3).

Remission was achieved by 2.6% of evaluable patients at t0+1 day, while this proportion increased to 38.9% in the group of evaluable patients at the end of hospitalization and to 47.8% at the end of observation.

Among patients who achieved remission at the end of hospitalization (visit 3; N = 23), 43.48% were no longer in remission at visit 4; furthermore, among patients who achieved remission at visit 4 (N = 32), 28.1% lost remission at visit 5 (of those with available assessment data).

Analysis of patients who achieved response according to the MADRS total score is reported in the Supplementary material.

3.4. Suicide risk

Assessment as per clinical judgment showed that, at t0+90 days, 79.1% of evaluable patients were in a negligible risk for suicide.

The MADRS-SI and the C-SSRS suicidal ideation item scores showed a meaningful reduction of suicidality symptoms at the end of hospitalization: indeed, both scores were very low at t0+90 days (0.8, SD 1.2 for MADRS-SI; 0.5, SD 1.0 for C-SSRS suicidal ideation score).

Differently from suicidal ideation, the feeling of hopelessness – assessed by BHS – did not recover, with a final mean (SD) score of 8.3 (5.4) on a 20-point scale (Supplementary Material).

3.5. Patient's health status and QoL

Patient-reported outcome measures, EQ-VAS and EQ-5D-5L, were utilized.

The EQ-VAS mean (SD) score – ranging from 0 to 100 – improved from 38.9 (31.8) at baseline (t0) to 66.9 (19.8) at t0+90 days (Fig. 4).

Assessment of QoL by EQ-5D-5L revealed that anxiety/depression and usual activity (e.g., work, study, housework, family or leisure activities) were the most impacted dimensions at t0, confirming the MDE. At t0+90 days, there was an improvement of the EQ-5D-5L scores, but the impact of depression on QoL was still clear: only approximately 30% of patients stated they were not anxious or depressed and approximately 50% confirmed they did not have problems doing everyday activities.

Table 2
Comprehensive treatment during observation in the ARIANNA study.

	Last treatment performed in the week before t0 (N = 117)	First treatment indication at t0 (N = 132)	Treatment between 8 days and 30 days after t0 (N = 130)	Treatment between 31 days after t0 and end of observation (N = 119)
Types of psychopharmacotherapy, *n* (%)				
Antidepressant	76 (65.0)	104 (78.8)	105 (80.8)	98 (82.4)
Anxiolytic/Hypnotic	49 (41.9)	73 (55.3)	73 (56.2)	68 (57.1)
Antipsychotic	46 (39.3)	90 (68.2)	90 (69.2)	82 (68.9)
Mood stabilizer/Lithium	38 (32.5)	60 (45.5)	61 (46.9)	62 (52.1)
Other	2 (1.7)	6 (4.5)	7 (5.4)	7 (5.9)
Integrated approach,*n*(%)				
Psychopharmacotherapy with psychosocial treatment	12 (10.3)	22 (16.7)	25 (19.2)	23 (19.3)

Note: A patient could have had more than one type of psychopharmacotherapy.
t0 = day on which the 'active suicidal ideation with intent' condition was defined/confirmed by the Investigator.

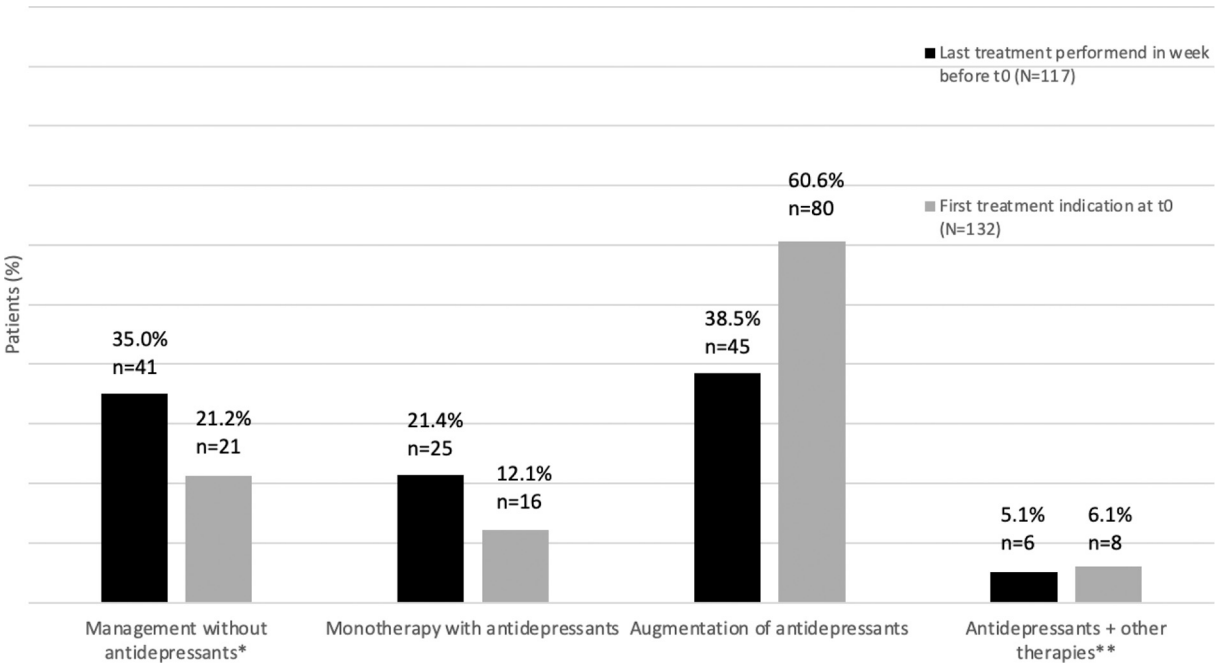
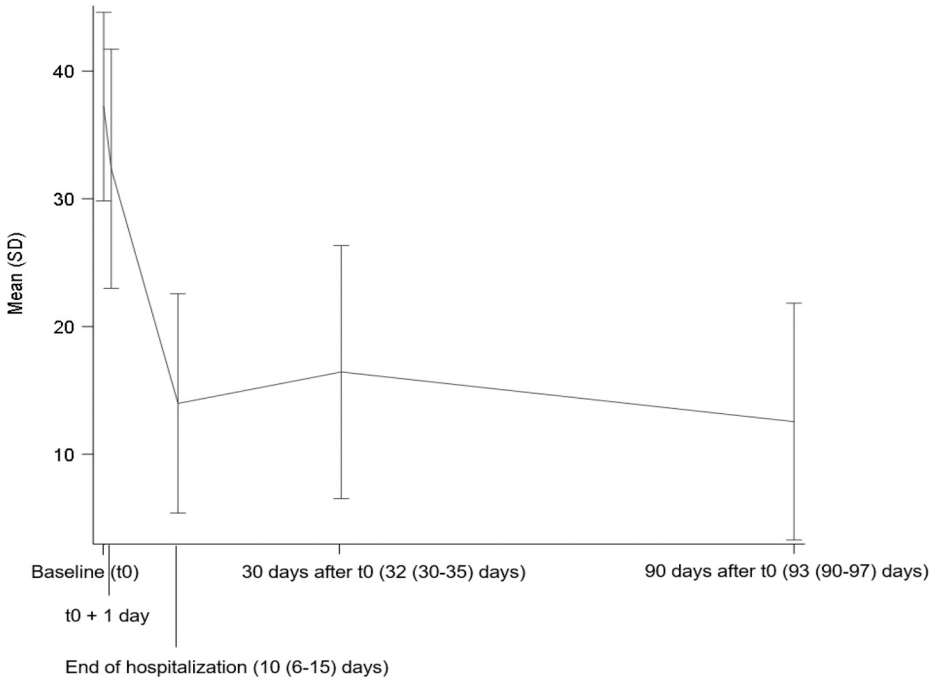


Fig. 2. Summary of pharmacological treatment strategies in the week before t0 and at t0 among patients included in the ARIANNA study.
t0 = day on which the 'active suicidal ideation with intent' condition was defined/confirmed by the Investigator.
*Among patients managed without antidepressants in the week before t0, 18 patients resulted without pharmacological and/or non-pharmacological treatment strategy performed.
**Including e.g., anxiolytics/hypnotics other than benzodiazepines and barbiturates.



Baseline (N=119)	t0+1 day (N=117)	End of hospitalization (N=90)	t0+30 days (N=90)	t0+90 days (N=90)
37.2 (7.4)	32.3 (9.4)	14.0 (8.6)	16.4 (9.9)	12.6 (9.3)

Fig. 3. Mean (SD) MADRS total score over time for patients with available data included in the ARIANNA study.
t0 = day on which the 'active suicidal ideation with intent' condition was defined/confirmed by the Investigator.
Abbreviation: SD, Standard Deviation

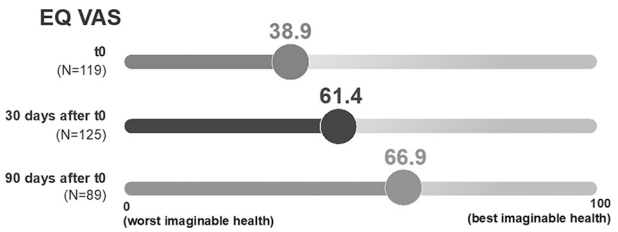


Fig. 4. EQ-VAS score for overall health status of eligible patients at different time-points.
t0 = day on which the 'active suicidal ideation with intent' condition was defined/confirmed by the Investigator. Visit 4 (t0 + 30 days) or visit 3 (end of hospitalization), if applicable. In case there were patients with EQ VAS available at both V3 and V4, EQ VAS at V4 was considered.
Abbreviation: EQ-VAS, European Quality of Life (EuroQol) Group Visual Analogue Scale.

3.6. Impact of patient's condition and treatment pathways on caregiver burden and distress

The IEQ (dichotomized) core module sumscore and the subscales' scores at baseline (t0) showed an overall distress caused by caregiving (mean [SD] score 8.6 [5.7]), with a higher relevance given to worrying for the patient (3.3 [1.8]) and urging (2.7 [2.5]).

The mean (SD) IEQ sumscore decreased over time, up to 3.9 (4.9) at the end of observation; worrying and urging remained the dimensions that mainly represented caregiver burden, with a mean (SD) subscale score of 1.5 (1.6) and 1.4 (2.4), respectively.

3.7. Safety profile

During the observation period, 14 (10.5%) patients experienced at least one AE, for a total of 16 AEs.

The most commonly reported AEs were weight gain (n = 3, 2.3%) and sedation (n = 2, 1.5%), both related to the current MDD comprehensive treatment according to medical judgment.

One serious AE, pneumonia, was reported and unrelated to the current MDD treatment. The occurrence of all treatment-related AEs is presented in the Supplementary Material.

No deaths were reported.

3.8. Healthcare resource utilization and costs

A total of 41 patients were eligible for the sub-study data analyses. Baseline socio-demographic characteristics were in line with those of the main study population (Table S10, Supplementary material).

Overall, 97.6% (n/N = 40/41) of evaluable patients had one or more general hospitalizations in the 3 years prior to enrollment in ARIANNA. Furthermore, 38 (92.7%) patients had 1 or more general hospitalizations during the year before enrollment. One or more hospitalizations related to psychiatric disorders or MDD in the 3 years before enrollment were observed in 92.7% and 61.0% of patients, respectively. Psychiatric disorders accounted for a mean (SD) of 1.8 (2.6) hospitalizations per patient in the prior 3 years, with a mean (SD) length of stay per episode of 16.4 (27.5) days.

When costs associated to resource use were analyzed, a higher average cost per patient was recorded in the year before enrollment in comparison with the other 2 years prior the aforementioned year: mean (SD) was 1780 € (2947 €) (Supplementary Material).

Psychiatric or neurological visits, pharmacological treatments, laboratory tests, and access to the emergency department also contributed to the medical resource consumption observed. The mean number of specialist visits per patient was 2.2 (SD 5.2), and the total number of patients that accessed EDs one or more times was 37 (90.2%), specially within the year before enrollment.

Hospitalizations, access to EDs, specialist visits, and laboratory tests undergone in the overall population were also collected in the prospective observation period of the study. In the sub-study cohort, the increasing trend in costs that was seen before enrollment was confirmed also in the follow-up period of 90 days: mean (SD) cost per patients was 2169 € (953 €) (Fig. S2, Supplementary Material).

The average cost per patient calculated in the sub-study cohort (N = 41) was confirmed by the calculations in the main study cohort (N = 133): mean (SD) cost per patients was 2112 € (1461 €). Of the total number of eligible patients in the main study, 75.9% (n = 101) had at least one in-patient hospitalization during the observation period (including those ongoing at enrollment visit), with a median (25th P-75th P) overall duration of 13.0 (8.0–20.0) days. Seventy-three (54.9%) patients accessed EDs at least once during the prospective observation period.

4. Discussion

Our study described the treatment strategies used in over 130 patients with MDD at confirmation of suicide ideation with intent, as per routine clinical practice in 24 Italian sites. Results of 3 months of observation showed that the pharmacological approach changed over time, with a high degree of heterogeneity and complexity. Most of the patients (>75%) were hospitalized. Antidepressants were the first-line treatment, with up to 80% of patients receiving them at the end of observation. Surprisingly, at confirmation of suicidality, 21% of patients were not treated with antidepressants. The study also showed that after a several weeks of treatment less than 50% of patients achieved remission, while symptoms of suicide risk were not completely resolved and patients did not achieve a satisfying QoL: EQ-VAS and EQ-5D-5L, showed only a moderate improvement in the overall health status of the patients.

The clinical characteristics of patients revealed that they were a fragile population: one in three patients had comorbidities other than psychiatric disorders, one in four patients reported a personal history of psychiatric disorders other than MDD (mostly anxiety disorders), and half of the overall patients experienced an emotionally stressful life event before the inclusion in the study, 32% of patients had a prior history of suicidal behavior. Even if controversial data in the literature exists, several studies showed that prevalence of suicidal ideation is higher in depressed patients with anxiety disorders, and that these conditions could be a weak predicting factor for future suicidal ideation and attempts [31]. Comorbidity with anxiety disorders should be at the forefront of clinical investigation as it may results in more complex major depressive disorder picture and symptoms severity [32,33].

The ratio of patients with moderate or severe MDEs was 1:1, meaning that the condition of psychiatric emergency due to suicidal risk is not strictly related to absolute depression severity. More than 70% of patients with available data were in a recurrent MDE, and the median duration of the current MDE was quite short, 1.2 months. As some researchers speculated, the recurrence of depressive episodes and the time spent in these may influence the risk of suicidal attempts over time [34]. For this reason, treating clinicians should pay attention to the clinical history of the patient, the symptoms, and the recurrence of depressive episodes, for an appropriate evaluation of the risks and, if needed, a proper decision-making process for treatment.

Furthermore, it is important to stratify response to treatment as in the case of seminal studies that investigate patients with TRD [35], pointing to the role of complex polypharmacological regimes [36] and relying on clinical risk factors to predict pharmacotherapy resistance; this may result in a cost-effective strategy in guiding the prescription of pharmacotherapy combined with psychotherapy [37].

Confirmation of suicidality changed the patient's management. Moreover, the study highlighted a large heterogeneity in comprehensive treatment patterns. Polypsychopharmacology was the most used strategy and showed an increased complexity during observation, with

consequent intensive resource utilization, including hospitalization.

Antidepressants, particularly SSRIs and SNRIs, were the first-line standard of care for patients with MDD and suicidal ideation with intent. After that, augmentation with mood stabilizers and/or antipsychotic drugs was the most systematic approach.

Of note is the fact the combination of pharmacological treatment and psychotherapy result in better outcomes in major depressive patients with suicide risk [38]. However, unexpectedly, the percentage of psychosocial treatment was low in our study, with only 19.3% of patients who were offered this option at the end of observation. This data is difficult to interpret; nevertheless, the low proportion of psychosocial interventions is documented in other similar studies, also in the European context [38]. The low utilization of psychosocial treatments could be due to the lack of (or difficult access to) such facilities in the sites of care/mental health departments and emphasizes an actual important unmet need in clinical practice for patients with MDD and suicidal ideation with intent [39].

The former data confirmed the results from previous international studies on patients diagnosed with MDD and suicidal ideation or attempt [11,18]: data from an U.S. population-based study and a European survey showed significant variability in the treatment received by patients, with antidepressants being the most prescribed treatment (61.9% and 77%, respectively), often in addition to various types of therapies.

Surprisingly, at t0, about one in five patients with depression at risk of suicide was not treated with antidepressants. These data could represent a very conservative approach, emphasizing the slight confidence in the prescription of antidepressants for this high-risk population. There are controversial data regarding the link between antidepressant use and the associated suicide risk. In contrast, studies show that untreated depression is closely related to a significant risk of suicide [40].

Our study confirmed no rapid relief of depressive symptoms according to the MADRS total score. A meaningful reduction in depressive symptoms was observed only at the end of hospitalization or 30 days after t0, despite a vast use of antidepressants and other pharmacological approaches. At the end of observation, <50% of patients achieved remission, and less than 80% of patients responded to treatment. Moreover, data showed that achieving and maintaining remission over time was difficult: more than 40% of remitters at the end of hospitalization were no longer in remission one month after enrollment, and almost one-third of remitters one month after enrollment were no longer in remission after 90 days of observation. These results highlight that current treatment strategies are inadequate for reaching rapid and maintaining long-term efficacy in many patients, representing a weakness of the pharmacological treatments.

Interestingly, while scores referring to suicidal thoughts and ideation seem to indicate a significant improvement of these symptoms from end of hospitalization onwards, the BHS scores, referring to hopelessness and thoughts/sentiments regarding the future, do not suggest a conclusive resolution of these important dimensions in the 90 days of observation. This is clinically relevant since hopelessness is associated to suicide risk, and the severity of suicidal intent has a stronger correlation with hopelessness than depression [41]. Furthermore, studies found that hopelessness appear to be associated with a higher probability of poor response to pharmacological treatment or psychotherapy for depression [42].

As expected, upon confirmation of suicidality, the patients' QoL and general health status was deteriorated. Nevertheless, an improvement was observed over time, even if the impact of MDD on the patients' lives was not completely resolved. In fact, compared to reference values in the Italian general healthy population (mean score 78.22; [43]), the ARIANNA patients reached a markedly lower score (mean score 66.9) at the end of observation.

Our observations support the idea of a difficult-to-treat population needing a treatment strategy to improve outcomes rapidly and effectively. The management of this population should include pharmacotherapies that could be useful in rapidly reducing depressive symptoms and, indirectly, suicidal ideation [39]. On the other hand, it is well known that current antidepressant drugs can take several weeks before they become effective. Therefore, patients may experience drug-related side effects during this time frame without perceiving their desirable, beneficial effects on psychiatric symptoms. Paradoxically, at that time, patients' conditions might even worsen, because the intervention started at a very delicate moment in their lives, when depression and suicidality symptoms are at a very high level [13,16,39,44]. Thus, future research on antidepressants should aim to identify drugs that may resolve symptoms quickly, possibly within hours. Recent findings from the ASPIRE studies, and the pooled analysis, highlighted the potential role of esketamine nasal spray as a rapid-acting antidepressant in treating depressive symptoms in a psychiatric emergency [4,45,46].

Furthermore, results for intranasal esketamine use in real life were also promising: . recent clinical experience with two patients affected by TRD and active suicidal ideation with intent, showed a rapid improvement in depressive symptoms and a successful resolution of the suicidal risk [47]. These results are valuable in a vulnerable population that requires an urgent evaluation and effective therapeutic approaches.

A further point of discussion is the social and economic burden of MDD with suicidality. The study confirmed that this condition also impacts caregivers, who perceive a high burden in terms of mental well-being, as demonstrated by previous studies [48–51]. In the ARIANNA study, an increase in healthcare costs has been measured in the 3 years leading to the diagnosis of MDD and suicidal ideation with intent. This increase continued in the 90 days after that episode. Of note, the length of hospitalization due to psychiatric reasons on average exceeded the 2-week mark and represented the most important resource in this analysis. Even if hospital admission is often required to save lives, we should be aware that it burdens patients and healthcare systems. Furthermore, studies showed that hospitalization itself is not effective, with high suicide rates observed in the first week after both admission and discharge [18,52,53].

Understanding the needs and pain of patients with MDD and suicidal ideation with intent is imperative in planning an appropriate strategy that may be personalized, as much as possible. This includes an effective pharmacological treatment but also understanding the benefit patients may get from psychosocial interventions and hospitalization.

Limitations of the study should be noticed. Since there is not clear consensus around specific tools for the diagnosis of MDD with suicidal ideation with intent, in our study, evaluation was only based on clinical judgment. The selected study sites were not randomly sampled from the Italian hospitals and clinics pool. We assume that many patients were at their first contact of mental health services and were not receiving antidepressant therapy or other non-antidepressant psychotropic medications. Our results should be, therefore, interpreted in consideration of this finding. The final patient sample cannot be generalized in the Italian population, so the external validity of the study results will refer to patients with similar characteristics to ours.

It is also noteworthy to acknowledge that MADRS scale was administered 1 day after the baseline visit. Although this represents a deviation from the standard use of this scale, we involved a study design originated in recent studies that investigated a target population similar to that described in the present study [45,46]. We speculate that the very low percentage of patients that experienced improvement in depressive symptoms in such a short time frame were probably benefitting from aspects such "placebo" like effect and empathic human support from clinical staff.

Of clinical importance and in light of limitations, we show that many patients (about 65%) were already on antidepressant treatment before t0 and for many patients, an augmentation treatment was initiated at t0. In this context, the remission rate at the end of hospitalization is probably not due only to effect of intervention introduced in the period from t0 to the end of hospitalization. Still, it should be interpreted for many patients as a continuation of treatment (given the non-interventional

nature of this study with inclusion criteria not restricted only to drug naïve patients).

Due to the chosen study design, we could not separate the single components of the integrated treatment (polypharmacotherapy, hospitalization, psychosocial intervention), or attribute specific effect to the single components and to the participation in the study, which could contribute to the patients' improvement. However, this is a valuable point for conducting further controlled studies.

The use of patient-reported outcomes may represent a bias; therefore, all scales and questionnaires were completed by patients and caregivers without involving Investigators unless minimal support was needed. Finally, in our study adverse events could have been underreported, since the safety analyses were a secondary objective of the ARIANNA study and were not intended to give a comprehensive assessment of the safety profile for each type of treatment used.

Nevertheless, this observational study described subjects in a difficult-to-study population for which there is a lack of international and local evidence. Our study cohort was not included in prior publications. To the best of our knowledge, the ARIANNA study is the first Italian observational analysis of this population and the first to produce administrative data with an original methodology, linking various data sources (hybrid design).

5. Conclusions

Patients with MDD and suicidal ideation with intent are a vulnerable population with a high disease burden, for which there is no standardized treatment approach. A history of psychiatric disorders, (included anxiety) and recurrence of depression episodes may determine a higher risk for suicidal behavior. Furthermore, feeling of hopelessness should also be carefully evaluated, since it is difficult to address and resolve with pharmacological therapies. This symptom also may contribute to a poor QoL. The comprehensive treatment used in this clinical population is mainly polypharmacological and delivered during the inpatient stay, increasing in complexity over time. The lack of specific treatments and recommendations for patients with MDD and suicidality contributes to use of wide and heterogeneous pharmacological approaches in clinical practice, which are often ineffective or have limited benefits for patients. More extensive in-depth studies on this population are required to understand the efficacy and safety of new treatments for this special population.

Healthcare providers need to be aware of these MDD patients' fragility. They should be involved in addressing the difficulties these patients face when depression emerges to reduce the risk of future suicidal ideation or attempts.

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Authorship

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

D. Delmonte, M. Adami, L. Simoni and R. Cipelli conceptualized the design of the study.

M. Pompili, B.M. Dell'Osso, G. Rosso, M. Amore, A. Bellomo, A. Mautone, E. Pilotto, S. Ramacciotti, M.I. Scardigli, were responsible for the patient enrollment and the collection of clinical data.

The ARIANNA Study Group contributed to the collection of clinical data.

L. Simoni and R. Cipelli performed the statistical analysis.

D. Delmonte, M. Pompili, L. Simoni and R. Cipelli carried out data interpretation and wrote the first draft of the manuscript.

B.M. Dell'Osso, G. Rosso, M. Amore, A. Bellomo, A. Mautone, E. Pilotto, S. Ramacciotti, M.I. Scardigli, G. Ascione, C. Sansone and M. Adami revised the manuscript and provided substantial comments.

All authors have approved the final version of the manuscript to be published.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

M. Pompili took part in advisory boards and educational activities on intranasal esketamine, receiving occasional fees for consultations or lectures by Janssen, which are unrelated to this article. In the last 2 years, he has received lectures or advisory board honoraria or engaged in clinical trial activities with Angelini, Lundbeck, Janssen, Pfizer, MSD, and Recordati.

B.M. Dell'Osso received lecture honoraria from Angelini, Lundbeck, Janssen, Pfizer, Neuraxpharm, Arcapharma, and Livanova.

G. Rosso received speaker/consultant fees for Angelini, Innova Pharma, Janssen, Lundbeck and Otsuka.

D. Delmonte was employed by Janssen-Cilag SpA.

M. Adami was employed by Janssen-Cilag SpA.

G. Ascione was employed by Janssen-Cilag SpA.

C. Sansone was employed by Janssen-Cilag SpA.

L. Simoni was employed by Medineos SURL (IQVIA Ltd.).

R. Cipelli was employed by IQVIA solutions SRL.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Due to the sensitive nature of the data collected in this study, it was assured raw data would remain confidential and would not be shared.

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Appendix A. Supplementary data

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