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Personality characteristics of volunteers in Phase 1 studies and likelihood of reporting adverse events

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Key words
Phase 1 studies – healthy subjects – volunteering – personality – adverse events

Abstract. Objective: To evaluate the personality characteristics of a group of participants in Phase 1 studies and to study the relation between the personality traits and the adverse events during participation. Methods: Study population consisted of 139 healthy volunteers to Phase 1 studies. Personality was assessed through the Revised NEO Personality Inventory (NEO-PI-R) and adverse events were monitored during participation. Results: Participants showed lower levels of Neuroticism ($p < 0.001$), and higher levels of Extraversion ($p < 0.001$) and Openness to Experience ($p < 0.001$) than the norm. In the Neuroticism domain, participants were lower in anxiety ($p < 0.001$), angry-hostility ($p < 0.001$), depression ($p < 0.001$), self-consciousness ($p < 0.001$) and vulnerability ($p < 0.001$), and higher in impulsiveness ($p < 0.001$). All facets of the Extraversion domain and all facets but "openness to esthetics" of the Openness to Experience domain were higher ($p < 0.001$) in the participants in relation to the norm. Participants were significantly lower ($p < 0.05$) on the overall Agreeableness domain, however, they were remarkably higher in altruism ($p < 0.001$) and trust ($p = 0.001$). Participants did not differ from the norm in the overall Conscientiousness domain, but they scored higher in competence ($p < 0.001$), achievement striving ($p = 0.001$) and self-discipline ($p < 0.001$). Females showed to report significantly more adverse events than males, and extraverted subjects showed to report less adverse events than introverted subjects. Conclusion: Participants who volunteer for Phase 1 studies, differ from the general population in their personality characteristics. Some personality characteristics may have an effect on the probability of reporting adverse events during participation. Therefore, defining a personality of a volunteer may assume significant importance in Phase 1 studies.

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Introduction

Participation in a clinical trial depends on previous subject's informed and free consent. It has been consistently reported in the literature [Almeida et al. 2007, Ayd and Calabresi 1972, Bigorra and Baños 1990, Meyer et al. 1995, Novak et al. 1977, Russel et al. 2000, Tishler and Bartholomae 2002, Van Gelderen et al. 1993] that financial compensation is the most important single motivation to participate in Phase 1 studies. However, all those who run Phase 1 studies empirically know that there are healthy subjects reasonably favored in socio-economic terms who are willing to participate and there are poorer subjects who completely reject the idea of participation. It means, therefore, that although financial compensation may be the key motivation for study participation in most subjects, it is not a sufficient motivation in other people. Admitting so, we have to accept that the decision to volunteer for study participation is complex and certainly influenced by other aspects than financial compensation.

Participation in Phase 1 clinical trials often involves confinement to an open-space ward with very low level of privacy for several days, close interaction with previously unknown people (clinical staff and other study participants), unaccustomed procedures some of them relatively invasive and painful (such as venous blood sampling), and the risk of expected or unexpected adverse events. Therefore, participation in Phase 1 clinical trials can be perceived as a challenging situation, and it can be presumed that some person-

ality traits may have an effect on the subject's willingness to volunteer. However, it is not yet known in what personality traits healthy volunteers actually differ from the general population [Tishler et al. 2005], and studies with the aim of identifying personality patterns for individuals who volunteer for Phase 1 clinical trials are needed.

Proving the existence of differences in personality characteristics of healthy volunteers in comparison with their peers in the normal population does not necessarily mean that such differences are clinically meaningful. Potential differences will be clinically important only if they interfere on the study outcomes and upon the interpretation of the results. Tolerability is systematically assessed in Phase 1 studies and is even the primary objective in entry-into-humans studies. The most common tolerability endpoint is the monitoring of adverse events throughout the study.

Our study aimed to contribute to fill the existing information gaps. Our main objective was to determine personality traits in which normal healthy subjects who volunteered for Phase 1 participation in our Human Pharmacology Unit differ from the population from where they were drawn. The second objective was to investigate potential correlations between the participants' personality traits and the likelihood of reporting adverse events during participation in Phase 1 studies.

Material and methods

Population

The study population consisted of 139 healthy subjects who volunteered for Phase 1 clinical trials at the Human Pharmacology Unit of BIAL (Portela and Co. SA, S. Mamede do Coronado, Portugal) with orally administered new chemical entities currently in clinical development as new medicines for epilepsy and Parkinson's disease. Main demographic and socio-economic characteristics of the study population are presented in Table 1. For 108 (77.7%) participants, that was their first and single participation in Phase 1 studies, 26 (18.7%) participants had previously participated in another Phase 1 study and further 5 (3.6%) subjects had previously participated in two Phase 1 studies. Studies involved confinement for up to 14 days and frequent blood drawings for pharmacokinetic analysis and safety procedures. All participants were selected according to the inclusion/exclusion criteria defined in the study protocols, which were similar between studies. Volunteers who admitted to smoke more than 10 cigarettes per day or to drink more than 14 units of alcoholic beverages per week were excluded.

The current research was approved by an Independent Ethics Committee (Comissão de Ética Independente da UFH, S. Mamede do Coronado, Portugal), and the clinical trials in which volunteers participated had been previously approved by the national Central Ethics Committee (CEIC – Comissão de Ética de Investigação Clínica, Lisbon, Portugal) and by the national drug regulatory authority (INFARMED – Instituto da Farmácia e do Medicamento, Lisbon, Portugal). Before any study started, subjects had one or more information meetings in which they received oral and written information regarding the proposed study, including details on study design, procedures, inconvenience or discomfort, precautions, possible adverse events and financial reward. The subjects had the opportunity to ask someone else's opinion before taking the final decision.

Assessments

Phase 1 participants were invited to anonymously complete a questionnaire regarding their demographic, socio-economic, habits and life-style characteristics (Table 1). Participants were also requested to complete the Revised NEO Personality Inventory (NEO-PI-R) [Costa and McCrae 1992]. The current dominant model in theory and research on personality proposes that personality is best described in terms of a hierarchical model with five main domains (personality 5-factor model) [Digman 1990, Costa and McCrae 1992, Goldberg 1990]. The NEO-PI-R is a highly regarded assessment of normal personality based on that personality model. It consists of 240 statements to which the respondents rate their level of agreement using a 5-point scale. Items are organized into the five broad domain scales, each of which is subdivided into six 8-item subscales. The five

Table 1. Descriptive statistics of main demographic and socio-economic characteristics.

Variable	Parameter	Male	Female	Total
Sample	N (%)	65 (46.8%)	74 (53.2%)	139 (100.0%)
Age (years)	Mean ± SD	25.9 ± 4.7	25.8 ± 5.3	25.9 ± 5.0
	Median	25	25	25
	Range	18 – 43	18 – 39	18 – 43
Ethnic group	Caucasian	93.8%	97.3%	95.7%
	Other	6.2%	2.7%	4.3%
Occupation	Student	58.5%	55.4%	56.8%
	Employed	32.3%	29.7%	30.9%
	Unemployed	4.6%	8.1%	6.5%
	Missing	4.6%	6.8%	5.8%
Scholarship completed	Master degree	3.1%	2.7%	2.9%
	Licensed	12.3%	17.6%	15.1%
	Bachelor	3.1%	6.8%	5.0%
	12 years	66.2%	60.8%	63.3%
	9 years	9.2%	4.1%	6.5%
	6 years	1.5%	1.4%	1.4%
	Missing	4.6%	6.8%	5.8%
Monthly net income in relation to the mean national net salary in the industry and services sector[#]	< 25%	27.8%	25.5%	26.6%
	25% – 50%	31.5%	36.4%	33.9%
	51% – 100%	25.9%	25.5%	25.7%
	101% – 150%	11.1%	7.3%	9.2%
	> 150%	3.7%	5.5%	4.6%
Civil status	Single	77.4%	78.3%	77.9%
	Married/living together	22.0%	10.1%	16.0%
	Divorced	0.0%	11.6%	6.1%
Smoking	Yes	33.3%	33.8%	33.6%
Coffee drinking	Yes	66.1%	66.7%	66.4%
Exercising/sports	Yes	77.4%	57.4%	66.9%
Alcohol drinking	Yes	63.1%	32.4%	46.8%

[#]approximately €1,000/month, net.

broad domains or factors measured by NEO-PI-R are the following: *Neuroticism (N):* predisposition to experience psychological stress and negative emotional states such as anxiety, anger, guilt, and depression; *Extraversion (E):* it is a dimension of sociability, liveliness, and cheerfulness; *Openness to Experience (O):* it involves active imagination, esthetic sensitivity, attentiveness to inner feelings, preference for variety, and intellectual curiosity; *Agreeableness (A):* tendency to be pleasant, sympathetic, cooperative, and altruistic in social situations; *Conscientiousness (C):* disciplined striving after goals and a strict adherence to principles, control of impulses, planning, organizing, ability to carry out a task. Each broad domain is divided into 6 specific personality traits or facets (Table 2).

The NEO-PI-R form S (self-administered) was used and had been previously validated for the Portuguese population and it was reported to have good psychometric properties [Pedroso-de-Lima and Simões 2000]. With the support of specific software [Rocha 2000],

Table 2. NEO-PI-R domains and traits: Mean ± SD direct punctuation and relative distribution of study volunteers in relation to the percentiles (P) of population norm, and statistical difference in relation to the population norm (n = 139).

NEO-PI-R domains facets	Direct punctuation		Percentile distribution					P value*	Participants versus norm
	Male	Female	Very high	High	Average	Low	Very low		
	Mean ± SD	Mean ± SD	P95 – 99	P70 – 90	P35 – 65	P10 – 30	P1 – 5		
N: Neuroticism	80.1 ± 17.8	87.9 ± 22.5	2.2%	14.4%	28.8%	37.4%	17.3%	< 0.001	Less
N1: Anxiety	15.8 ± 4.1	18.2 ± 4.4	2.2%	17.3%	27.3%	40.3%	12.9%	< 0.001	Less
N2: Angry-hostility	11.2 ± 3.3	12.5 ± 4.2	0.7%	14.4%	24.5%	47.5%	12.9%	< 0.001	Less
N3: Depression	12.2 ± 5.0	13.8 ± 5.3	1.4%	16.5%	23.7%	38.8%	19.4%	< 0.001	Less
N4: Self-consciousness	14.2 ± 3.9	15.3 ± 4.7	2.9%	16.5%	35.3%	32.4%	12.9%	< 0.001	Less
N5: Impulsiveness	16.7 ± 3.8	17.3 ± 4.4	10.1%	34.5%	26.6%	23.7%	5.0%	< 0.01	More
N6: Vulnerability	9.9 ± 3.4	12.2 ± 4.2	2.2%	13.7%	30.2%	42.4%	11.5%	< 0.001	Less
E: Extraversion	122.7 ± 13.4	122.2 ± 13.7	25.9%	47.5%	22.3%	4.3%	0.0%	< 0.001	More
E1: Warmth	23.4 ± 3.4	23.2 ± 3.4	8.6%	44.6%	29.5%	13.7%	3.6%	< 0.001	More
E2: Gregariousness	19.2 ± 4.6	19.8 ± 4.4	20.9%	36.0%	25.2%	18.0%	0.0%	< 0.001	More
E3: Assertiveness	16.5 ± 3.2	15.7 ± 3.5	10.8%	44.6%	30.2%	12.9%	1.4%	< 0.001	More
E4: Activity	18.5 ± 3.4	18.5 ± 3.6	19.4%	30.2%	31.7%	15.8%	2.9%	< 0.001	More
E5: Excitement seeking	21.8 ± 3.2	21.3 ± 4.0	21.6%	38.8%	33.1%	5.8%	0.7%	< 0.001	More
E6: Positive emotions	23.2 ± 3.7	23.4 ± 3.4	33.8%	49.6%	12.2%	4.3%	0.0%	< 0.001	More
O: Openness to Experience	119.3 ± 13.4	125.0 ± 13.8	11.5%	59.0%	25.9%	3.6%	0.0%	< 0.001	More
O1: Openness to Fantasy	20.3 ± 4.4	19.8 ± 4.6	10.8%	48.9%	28.1%	8.6%	3.6%	< 0.001	More
O2: Openness to Esthetics	21.1 ± 16.9	22.6 ± 4.1	7.9%	33.8%	38.8%	16.5%	2.9%	< 0.05	More
O3: Openness to Feelings	21.1 ± 3.0	21.7 ± 3.0	7.2%	44.6%	35.3%	12.2%	0.7%	< 0.001	More
O4: Openness to Actions	18.3 ± 3.0	19.1 ± 3.5	18.7%	46.0%	25.2%	10.1%	0.0%	< 0.001	More
O5: Openness to Ideas	20.7 ± 4.6	21.1 ± 4.0	17.3%	41.0%	33.8%	17.9%	0.0%	< 0.001	More
O6: Openness to Values	19.9 ± 3.3	20.8 ± 2.9	13.7%	55.4%	21.6%	9.4%	0.0%	< 0.001	More
A: Agreeableness	113.1 ± 19.3	119.4 ± 14.8	2.9%	15.8%	51.8%	23.7%	5.8%	< 0.05	Less
A1: Trust	19.1 ± 3.9	18.8 ± 4.4	5.0%	39.6%	25.9%	23.7%	5.8%	< 0.01	More
A2: Straightforwardness	17.4 ± 4.0	18.5 ± 3.9	2.2%	24.5%	36.7%	29.5%	7.2%	n.s.	Similar
A3: Altruism	22.2 ± 3.6	23.2 ± 3.7	8.6%	41.0%	25.9%	20.1%	4.3%	< 0.001	More
A4: Compliance	17.6 ± 4.0	17.4 ± 4.5	2.9%	19.4%	38.8%	28.8%	10.1%	< 0.05	Less
A5: Modesty	18.4 ± 3.7	19.5 ± 3.4	4.3%	15.1%	36.7%	37.4%	6.5%	< 0.01	Less
A6: Tender-mindedness	20.0 ± 2.9	21.9 ± 2.7	2.2%	27.3%	33.1%	35.3%	2.2%	< 0.05	Less
C: Conscientiousness	120.0 ± 19.5	121.9 ± 18.5	7.2%	31.7%	32.4%	25.2%	3.6%	n.s.	Similar
C1: Competence	21.7 ± 3.2	21.0 ± 3.3	9.4%	44.6%	25.2%	18.7%	2.2%	< 0.001	More
C2: Order	18.8 ± 4.8	19.7 ± 5.0	10.8%	25.2%	30.9%	27.3%	5.8%	< 0.05	More
C3: Dutifulness	22.4 ± 3.5	23.2 ± 3.3	4.3%	30.2%	33.1%	28.1%	4.3%	n.s.	Similar
C4: Achievement striving	20.7 ± 4.4	21.1 ± 3.7	11.5%	31.7%	28.8%	23.7%	4.3%	< 0.01	More
C5: Self-discipline	18.9 ± 4.8	19.6 ± 4.6	7.2%	38.8%	20.1%	23.0%	10.8%	< 0.001	More
C6: Deliberation	17.3 ± 4.3	17.2 ± 4.9	2.9%	22.3%	33.8%	32.4%	8.6%	< 0.05	Less

*χ^2 goodness-of-fit test

the individual results were interpreted by reference to the Portuguese population norms prepared for each scale and subscale, taking into attention the gender and age of the individual, and were displayed as direct scores and their conversion in percentiles of the norm. The software displays the percentiles (P) as units from P1 – P5 and from P95 – P99, the other punctuations are transformed in 5-unit interval percentiles (i.e. P10, P15, and so on, up to P90). Individual results for each domain and for each trait were then classified in the following categories: "very high" (scores within P95 and P99 of the normative group), "high" (P70 – 90), "average" (P35 – 65), "low" (P10 – 30) or "very low" (P1 – 5).

Adverse events (AEs) were monitored throughout the Phase 1 clinical trials according to the current standards: onset time and date, offset time and date, description, severity, causality assessment by the investigator, action taken and outcome. An AE was defined as any undesirable event occurring to a subject during the study, following the administration of an investigational product, whether or not considered to be related to the investigational product. Causal relationship between adverse event and study drug was performed by the investigator. Adverse events were coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA). For crossover studies, each study period was considered to be one "test". The following variables were derived: percentage of tests with AEs, percentage of tests with drug-related AEs, number of AEs/test, number of drug-related AEs/test, number of AEs/day of test, number of drug-related AEs/day of test, number of CNS-related AEs/test, number of CNS-related AEs/day of test.

Analyses

Statistical differences of Phase 1 study participants NEO-PI-R scores in relation to the population norm were assessed by the χ^2 Goodness-of-Fit Test. Spearman's ρ correlations were performed between the NEO-PI-R scores and the demographic characteristics and between the NEO-PI-R scores and the adverse events variables. All statistical analyses were performed with the Statistical Package for Social Sciences version 11.5 (SPSS Inc., Chicago, IL, USA). The criterion for statistical significance was set at an α error of 5% ($p < 0.05$), 2-sided.

Results

Personality characteristics of Phase 1 healthy volunteers in comparison to the normative population

Table 2 presents the summary statistics of the NEO-PI-R direct punctuation and the distribution of study volunteers by ranks of percentiles in relation to the normative population, for each personality domain and trait. Figure 1 displays graphically the results regarding the personality big domains.

Statistically significant differences between participants and the norm were found in most personality characteristics assessed. In the *Neuroticism* domain, participants were significantly lower in "anxiety" (tendency to apprehension, tension, fearfulness and worries), "angry-hostility" (tendency to experience anger, frustration and bitterness), "depression" (tendency to experience depressive affect), self-consciousness (shyness or social anxiety) and "vulnerability" (general susceptibility to stress, dependency), and significantly higher in "impulsiveness" (tendency to loose control).

All facets of the *Extraversion* domain are significantly higher in the participants than in the normative group: "warmth" (interest in and friendliness toward others), "gregariousness" (preference for the social contact), "assertiveness" (tendency to dominate, social ascendancy, determination and decision-taking), "activity" (pace of living), "excitement seeking" (search for environmental stimulation, risk-taking) and "positive emotion" (tendency to experience positive emotions, such as joy, happiness and love). All facets but "openness to esthetics" (appreciation of art and beauty) of the *Openness to Experience* domain were significantly higher ($p < 0.001$) in the participants than in the normative group: "openness to fantasy" (imagination), "openness to feelings" (sensitivity and receptivity to feelings and emotions), "openness to actions" (openness to novelty and new expe-

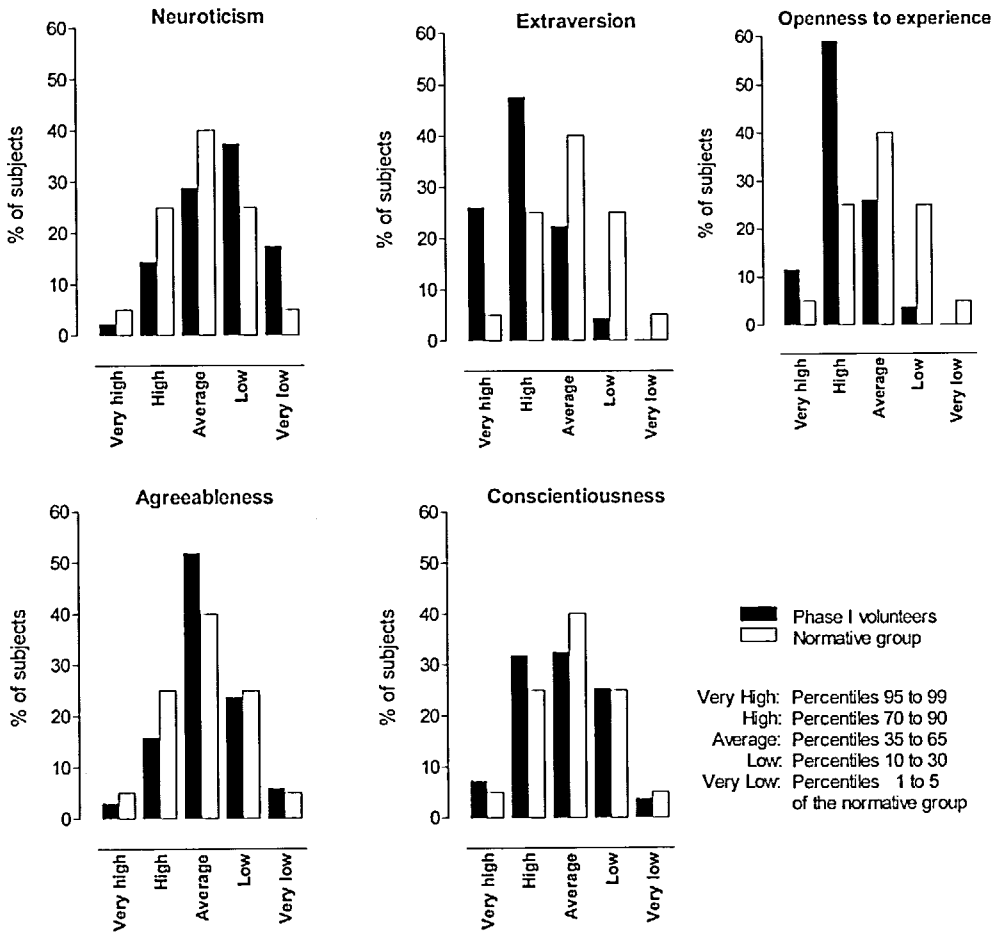

Figure 1. Distribution of participants in Phase 1 studies by percentiles group of the normative population.

riences on a practical level), "openness to ideas" (intellectual curiosity) and "openness to values" (tolerance, readiness to re-examine the social, political and religious values).

Overall, participants were significantly lower in the *Agreeableness* domain than the normative population. However, they were remarkably higher in "altruism" (social interest, active concern for the welfare of others) and "trust" (belief in the sincerity and good intentions of others). They were similar to the normal population in regard to "straightforwardness" (frankness and sincerity in expression) and were significantly lower in "compliance" (capacity to deal with interpersonal conflict), "modesty" (tendency to be humble and to play down own achievements) and "tendermindedness" (sympathy for others).

Participants did not differ from the norm in the global score of the *Conscientiousness* domain, but there were differences in some of its personality traits: participants scored significantly higher in "competence" (sense of mastery, believe in own efficacy), "order" (preference for clean and well organized environments, personal organization), "achievement striving" (need for personal achievement, ambition and sense of direction) and "self-discipline" (capacity to begin and complete tasks, despite boredom or distractions), and significantly lower in "deliberation" (tendency to think and plan carefully before speaking or acting), they were similar in "dutifulness" (reliability, importance of fulfilling moral or ethical obligations).

Correlations between the different personality domains and traits were investigated. Regarding the personality domains, inverse correlations were found between *Extraversion* and *Neuroticism* ($R_S = -0.244$, $p < 0.01$), between *Conscientiousness* and *Neuroticism* ($R_S = -0.626$, $p < 0.001$), and *Agreeableness* and *Neuroticism* ($R_S = -0.190$, $p < 0.05$), a direct correlation was found between *Extraversion* and *Openness to Experience* ($R_S = 0.383$, $p < 0.001$). Significant intercorrelations were

Table 3. Adverse events with a frequency >1.0%, coded according to the MedDRA Lowest Level Term (LLT).

Adverse event LLT	Frequency
Dizziness	13.2%
Somnolence	6.2%
Headache	6.2%
Nausea	2.9%
Tremor of hands	2.9%
Dysmenorrhea	2.9%
Epistaxis	2.9%
Frontal headache	2.5%
Pharyngitis	2.1%
Rhinitis	2.1%
Rhinorrhea	2.1%
Ecchymosis	2.1%
Myalgia of lower extremities	1.7%
Nasopharyngitis	1.7%
Paresthesia tongue	1.7%
Temporal headache	1.7%
Vomiting	1.2%
Loose stools	1.2%
Anorexia	1.2%
Erythema	1.2%
Erythematous rash	1.2%
Hematoma	1.2%
Localized erythema	1.2%
Pruritus NOS	1.2%

also found between several personality traits. Overall, there was a high agreement of the intercorrelations between the different personality domains and traits found in our population and the intercorrelations described in the NEO-PI-R technical manual [Pedroso-de-Lima and Simões 2000], which supports the validity of our results.

Reporting of adverse events

A total of 239 adverse events (AEs) were reported in the 317 individual study periods (tests). Mean ± SD number of days per test was 9.6 ± 8.5 (range 3 – 41 days). Approximately 41% were "nervous system disorders", according to the system organ class (SOC) classification of the MedDRA dictionary. Table 3 presents the mostly reported AEs coded according to the "lowest level term" (LLT) of the MedDRA dictionary. The mean ± SD number of AEs per test was 0.76 ± 1.2 (range 0 – 6), of drug-related AEs per test was 0.54 ± 1.0 (range 0 – 5), of AEs per day of test was 0.15 ± 0.20 (range 0.0 – 1.0), of drug-related AEs per day of test was 0.10 ± 0.16 (range 0.0 – 0.8), of CNS-related AEs per test was 0.40 ± 0.84 (range 0.0 – 5.0), and of CNS-related AEs per day of test was 0.08 ± 0.15 (range 0.0 – 0.8).

At least 1 AE was reported in 43.5% of tests with male subjects and in 62.3% of tests with female subjects. Among the demo-socio-economic variables assessed, gender was the single variable that showed to influence the likelihood of adverse events. In relation to males, females showed higher percentage of tests with AEs ($R_S = 0.169$, $p < 0.05$), higher percentage of tests with drug-related AEs ($R_S = 0.209$, $p < 0.01$), higher number of AEs per test ($R_S = 0.215$, $p < 0.01$), higher number of drug-related AEs per test ($R_S = 0.230$, $p < 0.01$), higher number of AEs per day of test ($R_S = 0.190$, $p < 0.01$), higher number of drug-related AEs per day of test ($R_S = 0.231$, $p < 0.01$), higher number of CNS-related AEs per test ($R_S = 0.184$, $p < 0.05$), and higher number of CNS-related AEs per day of test ($R_S = 0.193$, $p < 0.01$).

Statistical significant linear correlations were found between the following NEO-PI-R personality traits of the *Extraversion* domain and the defined adverse events variables: a negative linear correlation between "warmth" and probability of AEs, attaining significance ($p < 0.05$) in the number of AEs/day of test ($R_S = -0.174$, $p < 0.05$), number of CNS-related AEs/test ($R_S = -0.197$, $p < 0.05$), and number of CNS-related AEs/day of test ($R_S = -0.204$, $p < 0.05$); a negative linear correlation between "gregariousness" and probability of AEs, being significant in number of CNS-related AEs/test ($R_S = -0.209$, $p < 0.05$) and number of CNS-related AEs/day of test ($R_S = -0.205$, $p < 0.05$); a negative linear correlation between "excitement seeking" and probability of AEs, being significant in percentage of tests with AEs ($R_S = -0.175$, $p < 0.05$), number of AEs/test ($R_S = -0.209$, $p < 0.05$), number of drug-related AEs/test ($R_S = -0.179$, $p < 0.05$), number of AEs/day

of test (R_S = –0.223, $p < 0.05$), number of drug-related AEs/day of test (R_S = –0.176, $p < 0.05$), number of CNS-related AEs/test (R_S = –0.220, $p < 0.05$), and number of CNS-related AEs/day of test (R_S = –0.219, $p < 0.05$).

Discussion

This study shows that normal healthy subjects who volunteer for participation in Phase 1 clinical trials are significantly different from the population from where they are drawn in many personality traits. This study also suggests that few of the reported differences may have an impact in the assessment of tolerability (reporting of adverse events), which is an usual endpoint in Phase 1 clinical trials.

The relevance of studies in healthy volunteers to the prediction of effects in patients has been discussed for many years [Meyer et al. 1995]. However, for reasons of convenience and safety, studies in healthy subjects still remain the paradigm of Phase 1 studies during the clinical development program of new medicines. Although it is accepted that healthy volunteers do not necessarily represent the target population, it is assumed that they should represent at least their age group [Pieters et al. 1992]. However, our study corroborates data from other studies [Meyer 2001] suggesting that participants in Phase 1 clinical trials are a self-selected population which differs from the general population from where they are drawn.

In Phase 1 studies, healthy volunteers are usually characterized according to age, gender, ethnicity, body weight and height, and, less often, by their life-style characteristics (mainly smoking, exercising, alcohol beverages and drugs) [Meyer 2001]. If other factors, namely psychological characteristics (e.g. personality traits, motivations and emotional states), prove to have a potentially significant effect on the study endpoints (e.g. central effects or adverse effects of drugs, and possibly also their pharmacokinetics), such factors should be taken into consideration and stratification of subjects according to such factors may be justifiable while performing randomization to the different treatment groups. That means, if a correlation between certain personality traits and the study outcomes is proven, then it may be justifiable to submit healthy volunteers to psychological tests [Meyer 1995].

Differential psychopharmacological investigations performed by Meyer and colleagues [1992] suggested that both pharmacokinetics and pharmacodynamics can be influenced by the predominant personality traits of the subjects, and there is also a suspicion that personality characteristics might have an influence on the likelihood of reporting symptoms [Meyer et al. 2000]. However, little is known about those personality traits that actually have a relevant effect on the study outcomes. Therefore, besides the investigation of the personality traits in which Phase 1 volunteers differ from their peers in the normal population, we also explored the quantitative relationships between the personality traits and the adverse events reported by volunteers during Phase 1 participation. The results suggest that more extraverted subjects report less adverse events. Therefore, taking into account that study participants represent a self-selected population of more extraverted subjects than normal population, it may be concluded that:

- globally, the self-selection may cause a decrease in the likelihood of reporting adverse events during Phase 1 studies,
- in the case of studies in more than one group of participants, between-groups imbalances in subjects' extraversion may generate biased results when results in the different groups are compared.

Besides the inverse correlation between the reporting of adverse events and the extraversion personality domain, no other statistical correlations were found. However, the results should be interpreted with caution because they do not allow to exclude the hypothesis of other correlations. For example, there is some evidence that healthy subjects with high anxiety tend to report more adverse events than healthy subjects with low anxiety [Tishler et al. 2005]. In our study, we have found a trend for a positive correlation between neuroticism and the likelihood of adverse events, but it did not attain clinical significance. The lack of statistical significance may be due to the relatively low sample size and to the fact that our population is a self-selected sample of healthy subjects low in neuroticism. The underrepresentation of sub-

jects high in anxiety decreases the chance of potential correlations between neuroticism and likelihood of reporting adverse events to become apparent. The same limitation is valid for other personality traits in which the Phase 1 study population showed to differ markedly from the general population. Therefore, no definite conclusion can be obtained from the lack of statistically significant correlations between the reporting of adverse events and the personality traits in which Phase 1 participants differ significantly from the normal population. To adequately clarify the question of the effect of the different personality on the reporting of adverse events, it would be necessary to design prospective comparative studies in which subjects would be stratified according to their personality characteristics. However, such studies appear to be hard to implement, because participation must be based on the informed consent and volunteers with certain personality characteristics (e.g. high in neuroticism) tend to refuse participation.

Conclusion

Participants who volunteer for Phase 1 studies differ from the general population in several personality characteristics. It appears that some differences in personality traits may be of clinical significance by affecting the study outcomes, such as the reporting adverse events. Therefore, defining a personality of a volunteer may assume significant importance in Phase 1 studies.

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