Age and Sex as Moderators of the Placebo Response – An Evaluation of Systematic Reviews and Meta-Analyses across Medicine

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Key Words

Placebo response · Age · Sex · Randomized controlled trials · Meta-analyses

Abstract

Predictors of the placebo response (PR) in randomized controlled trials (RCT) have been searched for ever since RCT have become the standard for testing novel therapies and age and gender are routinely documented data in all trials irrespective of the drug tested, its indication, and the primary and secondary end points chosen. To evaluate whether age and gender have been found to be reliable predictors of the PR across medical subspecialties, we extracted 75 systematic reviews, meta-analyses, and meta-regressions performed in major medical areas (neurology, psychiatry, internal medicine) known for high PR rates. The literature database used contains approximately 2,500 papers on various aspects of the genuine PR. These 'meta-analyses' were screened for statistical predictors of the PR across multiple RCT, including age and gender, but also other patient-based and design-based predictors of higher PR rates. Retrieved papers were sorted for areas and disease categories. Only 15 of the 75 analyses noted an effect of younger age to be associated with higher PR, and this was predominantly in psychiatric conditions but not in depression, and internal medi-

cine but not in gastroenterology. Female gender was associated with higher PR in only 3 analyses. Among the patient-based predictors, the most frequently noted factor was lower symptom severity at baseline, and among the design-based factors, it was a randomization ratio that selected more patients to drugs than to placebo, more frequent study visits, and more recent trials that were associated with higher PR rates. While younger age may contribute to the PR in some conditions, sex does not. There is currently no evidence that the PR is different in the elderly. PR are, however, markedly influenced by the symptom severity at baseline, and by the likelihood of receiving active treatment in placebo-controlled trials.

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Introduction

Since the introduction of double-blinded and randomized placebo-controlled trials (RCT) in pharmacology and drug development in the middle of the last century, attempts have been made to identify and characterize patients that respond to placebo application with symptom improvement during an RCT [1]. At the same time, ethical concerns have requested to limit the number of patients exposed to placebo to a minimum and to pro-

vide the best treatment available to those seeking health care for acute and chronic conditions [2].

The consequences resulting from this dilemma are numerous design variants that were developed to overcome RCT limitations: single and multiple crossover designs, placebo- and drug run-in phases, randomized and blinded run-ins and withdrawals, enrichment designs with more patients randomized to the drug than to placebo, cluster randomization, step-wedge design, registry trials, Zelen design, and sequential parallel comparison designs, to name just a few [3]. They all have advantages and pitfalls in minimizing the placebo effects in RCT [4].

At the same time, psychologists and trialists have attempted to profile placebo responders in RCT, with much less success than initially thought [5]. Among the many personality traits that have been tested for prediction of placebo responses (PR) specifically in experimental settings, a few have been able to allow generalization across conditions and diseases [6], and certainly most – if not all – have never been tested in large-scale RCT for obvious reasons: if they would demonstrate an identifiable and substantial subset of patients that has to be excluded, this would pose the indication of the drug under testing at risk.

Biomarkers of the PR, especially genetic traits may be the future (e.g. COMT in irritable bowel syndrome, IBS, patients [7]), but currently the list is rather small [7–10], and it appears unlikely that a single genetic polymorphism, e.g. of the oxytocin pathway [11, 12], may account for all PR in all medical and clinical conditions.

Under these circumstances, it is not surprising that age and gender issues have repeatedly been named as important contributors (mediators or moderators) to the PR in RCT as they are recorded and documented in all RCT performed; especially the PR in different age groups has frequently been reviewed [13–15]. We recently [16] screened the literature with respect to the question whether children and adolescents exhibit higher PR than adults, and found at least some evidence to supporting this position. Experimental data however, devoted to this question come to the opposite conclusion [17].

Very few data but mostly speculation exist with respect to the question what happens to the PR in the elderly [18]. A narrative review in *Gerontology* discusses potential outlines in general; however, it does not come to a firm prospect and prediction [19], and experimental data, e.g. testing susceptibility to placebo analgesia procedures across the older age ranges, do not exist.

Theoretically, one may assume three models: either the child-to-adolescent-to-adulthood decrease in the PR

that has been proposed before [16] continues (model 1), or it stabilizes and no further change in the PR is noted with reaching adult life (model 2), or the function reverses (model 3). Model 1 would use a ‘continuous learning’ assumption that blocks the PR in the elderly to operate due to a longer history of successful and failed medicinal interventions. Model 2 (stable PR once adulthood is reached) assumes the major driver of the PR to occur during childhood, when the learning capacity is maximal and expectations are the highest. Model 3 finally assumes a cognitive decline to occur with senescence that may also affect expectations for help to increase again. None of these models is currently supported by strong empirical evidence, and they may vary across diseases and systems.

To approach an answer to this question, we set out to evaluate current evidence for a role of age – and gender – in re-analyses of RCT, either as systematic reviews, or as methodologically firm meta-analyses or meta-regressions. In addition to checking for age and gender contributions to the PR, we were interested in other patient- or design-based factors that would be associated with higher PR across different medical conditions.

Methods

Since 2004, we searched PubMed for articles using the search term ‘placebo’ both retrospectively and prospectively to select papers dealing with the placebo effect.

For all approximately 100,000 citations retrieved in 2004, we (K.W., P.E.) screened their titles and abstracts retrospectively and excluded papers describing placebo-controlled trials of individual drugs and other medical interventions that ‘only’ assessed differences between drug and placebo for evaluation of therapeutic benefits of the therapy. We also excluded meta-analyses of placebo-controlled trials and respective reviews. After exclusion of letters and editorials, we were left with approximately 1,000 papers (or approximately 1% of all papers screened) that discussed different aspects of the PR and/or placebo effects in different medical and psychological subspecialties. These were predominantly experimental data (exploring the different mechanisms of the PR) and reviews, systematic reviews, re-analyses and meta-analyses of RCT data. PDFs of these papers were retrieved and stored in an End-Note database.

Since 2004, we prospectively screen all papers published on a weekly basis ever since (total paper count: 170,855 as of April 4, 2014) using the same search term ‘placebo’. In 2010, we added the search term ‘nocebo’ (230 citations as of April 4, 2014). We occasionally added papers that explored and discussed psychosocial contributions to placebo-like effects even without using the term placebo, e.g. Kunz et al. [20].

This database currently contains approximately 2,500 papers of various aspects of the placebo and nocebo response in medicine and beyond. The distribution of these papers on the genuine placebo and nocebo effects between 1960 and 2014 is depicted in

Fig. 1. Yearly publication of genuine papers on the placebo and nocebo response in PubMed between 1950 and 2012.

figure 1, and demonstrates an exponential increase, similar to the increase seen in the remaining placebo literature.

This database was hand-searched by all authors for systematic reviews, meta-analyses, and meta-regressions of the placebo effects and its determinants (mediators, moderators) in various medical specialties, supplemented by papers found in these papers and entered into our database. This way, we identified 75 systematic reviews, meta-analyses and meta-regressions that were used for this systematic review.

Each of these papers was then screened for whether age and gender were included in the analysis, and whether they were explicitly found as moderators of the PR in the placebo arm of respective trials, irrespective of the type of statistical analysis (ANOVA, regression, multiple regression, meta-regression) that was used to identify it. To not over- or underestimate the respective findings, we categorized the potential contribution of age and sex with ‘yes’ or ‘no’ only, based on the paper’s own evaluation.

We also noted whether and which other patient or design factors in the trials were found to contribute to the size of the PR.

Results

The 75 systematic reviews, meta-analyses and meta-regressions were sorted into 6 disease groups: neurological diseases (Parkinson’s disease, restless leg syndrome, epilepsy, excluding pain: 9 papers), pain syndromes (migraine, neuropathic pain, fibromyalgia, excluding visceral pain: 13 papers), psychiatric diseases [schizophrenia, mania, psychosis, attention-deficit hyperactivity disorder (ADHD), addiction, excluding depression: 17 papers], de-

pression (15 papers), gastrointestinal disorders [IBS, functional dyspepsia (FD), inflammatory bowel diseases: 12 papers], and other mixed disorders [asthma, overactive bladder (OAB), hypertension, allergy, chronic fatigue, sleep problems: 10 papers]; one paper meta-analyzed 2 diseases.

It should be noted that these 75 analyses (which we will refer to collectively as ‘meta-analyses’ in the following) used quite different methodologies for their respective analyses on the one hand, which makes a direct comparison difficult if not impossible. On the other hand, the papers selected from the body of literature (mostly randomized, placebo-controlled trials, sometimes including comparator trials with two or more drugs) may substantially overlap within a condition but were frequently based of different selection and quality criteria. It is therefore conceivable that in some conditions (e.g. in depression) similar mediators and moderators are reported by different analyses, while in other cases, analyses may not have been able to replicate previous analyses.

Furthermore, only a minority of all papers ($n = 20$) were based on individual patient data available, while all other are referring to the published reports (or data reports to the drug approval authorities) that usually only contain means and standard deviations of the data on the age of patients, and percentage of males/females in the respective treatment groups.

Major findings within and across clinical conditions will subsequently be discussed for each of the medical

Table 1. Meta-analyses of RCT in neurological disorders

First author	Year	Ref.	n	Disease	Age	Sex	PR is higher with	PR is also higher with
Burneo	2002	21	31	epilepsy	no	NR		no other factor identified
Rheims	2008	22	32	epilepsy	yes	no	lower age	no other factor identified
Schmidt	2013	23	3*	epilepsy	yes	no	higher age	lower baseline severity
Fulda	2008	24	36	RLS	no	no		longer trial duration
Ondo	2013	25	6*	RLS	no	yes	female sex	lower baseline severity
Goetz	2000	26	1*	Parkinson	no	no		no other factor identified
Goetz	2008	27	2*	Parkinson	yes	no	higher age	lower baseline severity
Goetz	2008	28	11*	Parkinson	no	no		higher baseline severity
Ondo	2007	29	2*	Parkinson	yes	no	higher age	no other factor identified

RSL = Restless leg syndrome; NR = not reported; n = number of studies analyzed; asterisk indicates that individual data were available.

Table 2. Meta-analyses of RCT in pain disorders

First author	Year	Ref.	n	Disease	Age	Sex	PR is higher with	PR is also higher with
Diener	1999	30	15	migraine	NR	NR		higher drug chance
Macedo	2006	31	98	migraine	no	no		European studies
Macedo	2008	32	32	migraine	NR	NR		European studies
Ho	2009	33	8	migraine	yes	no	lower age	lower prior triptan use
Sun	2013	34	7	migraine	yes	NR	lower age	early response
Meissner	2013	35	79	migraine	no	no		type of placebo
Averbuch	2001	36	16	dental pain	NR	no		no other factor identified
Quessy	2008	37	35	neuropathic pain	NR	NR		higher drug chance
Kamper	2008	38	44	pain	NR	NR		no other factor identified
Zhang	2008	39	193	osteoarthritis	no	no		lower baseline severity
Häuser	2011	40	72	fibromyalgia	no	no		lower baseline severity
Häuser	2011	40	70	DPN	no	no		lower baseline severity
Capurso	2012	41	7	pancreatitis	no	no		more study sites

DPN = Diabetic polyneuropathy; NR = not reported; n = number of studies analyzed.

subgroups, with a special emphasis of whether or not age and gender have been noted as contributing factors to the size of the PR.

Neurological Trials (Excluding Pain)

Table 1 reports results from 9 meta-analyses in Parkinson's disease (n = 4), restless leg syndrome (n = 2), and epilepsy (n = 3). Two Parkinson's disease analyses noted higher PR with older age among adults [27, 29], while of the two analyses that expressively investigated age aspects (children vs. adults) in epilepsy, only one [22] could substantiate that the PR is double as high in children (19%) compared to adults (9.9%) while the other found the opposite [23]. Only one of the 7 reports noted higher PR in females [25].

Among the other factors identified to predict higher PR in more than one analysis are lower baseline severity of epilepsy, restless leg symptoms, and PD [23, 25, 27], but one analysis [28] found higher baseline severity to be associated with higher PR in PD.

Pain Trials

The meta-analyses of pain trials across different pain conditions include migraine (n = 6), neuropathic pain (n = 3), and dental pain, osteoarthritis, fibromyalgia, and pain in pancreatitis (n = 1 each; table 2). In none of the analyses was gender noted as the predictor of the PR, and in only two migraine analyses [33, 34] was age noted as a predictor.

Table 3. Meta-analyses of RCT in psychiatric disorders

First author	Year	Ref.	n	Disease	Age	Sex	PR is higher with	PR is also higher with
Woods	2005	42	32	schizophrenia	no	no		higher chance of drug
Kemp	2010	43	28	schizophrenia	NR	NR		lower baseline severity
Mallinckrodt	2010	44	27	schizophrenia	no	yes	female sex	higher change of drug
Chen	2010	45	31	schizophrenia	yes	no	lower age	lower baseline severity
Potkin	2011	46	3*	schizophrenia	no	no		lower baseline severity
Agid	2013	47	50	psychosis	yes	no	lower age	higher baseline severity
King	2013	48	1*	autism, children	no	no		lower symptom severity
Sysko	2007	49	20	bipolar mania	NR	NR		recent studies
Yildiz	2011	50	38	bipolar mania	yes	yes	higher age, female sex	recent studies
Cohen	2010	51	40	OCD, anxiety	yes	no	lower age	lower baseline severity
Newcorn	2009	52	10	ADHD children	yes	no	lower age	medication-naïve patients
Waxmonsky	2011	53	2*	ADHD	yes	no	higher age (adults)	higher baseline severity (adults only)
Buitelaar	2012	54	2*	ADHD adults	yes	no	lower age	higher baseline severity
Blom	2014	55	10*	BED	no	no		lower baseline severity
Green	2010	56	107	smoking	NR	NR		no industry support
Litten	2013	57	48	alcohol	yes	NR	lower age	recent studies
Moore	2012	58	28	addictions	NR	NR		no other factor identified

BED = Binge eating disorder; NR = not reported; n = number of studies analyzed; asterisk indicates availability of individual patient data.

Lower baseline pain intensity was noted as a predictor in 3 analyses [39, 40]. Among study characteristics, a higher chance for drugs resulted in higher PR in two instances [30, 37], European studies were reported to have higher PR as compared to studies in the US [31, 32], as well as a higher number of study sites [41].

Psychiatric Trials (Excluding Depression)

Of the 17 meta-analyses in psychiatric disorders, trials in schizophrenia (n = 6) received the most attention, followed by addiction therapy (n = 3), ADHD (n = 3), bipolar mania (n = 2), and autism, binge eating disorders, and obsessive-compulsive disorder/anxiety (OCD; n = 1 each; table 3). Five analyses were based on individual data.

Eight analyses reported age-related differences in the PR, however with different trends. Younger age was associated with higher PR in schizophrenia [45, 47], OCD [51], ADHD in children and adults [52, 54], and treatment of alcohol dependence [57], while in bipolar mania and one adult ADHD analysis, higher PR was associated with higher age [50, 53]. Two analyses only noted higher PR in females [44, 50].

Lower baseline severity of symptoms was the most frequently noted patient-based predictor of high PR (5 analyses [43, 45, 46, 51, 55] across all conditions), while in ADHD in adults, higher baseline severity was associated

with higher PR [53, 54], similar to schizophrenia [47]. More recent trials produced higher PR [49, 50, 57], as did a higher randomization ratio to drug [42].

Depression Trials

Depression trials represent the largest single clinical entity that has been meta-analyzed for predictors of the PR; in fact, increasing PR rates in more recent trials were noted first in depression [60] and mark the starting point for the increase in placebo research in the early years of the 21st century (see above, fig. 1).

The 15 meta-analyses included in table 4 include 3 with individualized data [59, 69, 73].

Only one analysis [65] noted an influence of age on the PR (higher PR in patients below age 65), none reported an influence of sex on the PR.

Among the patient-based characteristics of high PR, lower baseline severity [59, 64–66, 72] was noted as predictive, as was worsening of symptoms during screening and study start [62], and treatment-naïve patients [69]. In contrast to most other meta-analyses, one analysis noted higher baseline severity of symptoms to be associated with higher PR [61].

In more recent trials [60], a higher randomization ratio [68] and European studies [63] were linked to higher PR. Another design factor associated with higher PR was a higher number of study visits [70, 73].

Table 4. Meta-analyses of RCT in depression

First author	Year	Ref.	n	Disease	Age	Sex	PR is higher with	PR is also higher with
Brown	1992	59	1*	depression	no	no		lower baseline severity
Walsh	2002	60	75	depression	NR	NR		recent studies
Khan	2002	61	45	depression	NR	NR		higher baseline severity
Evans	2004	62	4	depression	no	no		symptom worsening before start
Stein	2006	63	12	GAD, PD, MDD	no	no		European studies
Kirsch	2008	64	35	depression	no	NR		lower baseline severity
Papakostas	2009	65	182	depression	yes	NR	lower age (<65 years)	lower baseline severity
Bridge	2009	66	12	depression, children	NR	no		lower baseline severity
Brunoni	2009	67	41	depression	no	no		rTMS as add-on therapy
Sinyor	2010	68	91	depression	NR	NR		higher chances for drug
Hunter	2010	69	1*	depression	no	no		treatment-naïve patients
Rutherford	2011	70	11	depression, children	no	NR		higher number of study visits
Gueorguiva	2011	71	7	depression	no	no		no other factor identified
Khin	2011	72	81	depression	NR	NR		lower baseline severity
Mancini	2014	73	14*	depression	no	NR		higher number of study visits

GAD = General anxiety disorder; PD = panic disorder; MDD = major depression disorder; rTMS = repetitive transcranial magnetic stimulation; NR = not reported; n = number of studies analyzed; asterisk indicates availability of individual patient data.

Table 5. Meta-analyses of RCT in gastrointestinal disorders

First author	Year	Ref.	n	Disease	Age	Sex	PR is higher with	PR is also higher with
Ilnyckyj	1997	74	38	IBD	NR	NR		higher number of study visits
Su	2004	75	21	IBD	no	no		higher number of study visits
Renna	2008	76	16	IBD	no	no		longer follow-up
Pitz	2005	77	84	IBS	yes	no	lower age	higher number of study visits
Patel	2005	78	45	IBS	no	no		lower number of study visits
Dorn	2007	79	19	IBS	no	no		higher number of study visits
Ford	2010	80	73	IBS	no	no		European studies
Talley	2006	81	4*	functional dyspepsia	no	no		inconsistent symptoms
Enck	2009	82	1*	functional dyspepsia	no	no		improvement during run-in
De Craen	1999	83	79	duodenal ulcers	NR	NR		higher application frequency
Yuan	2009	84	36	gastric ulcers	no	NR		previous gastrointestinal history
Cremonini	2010	85	24	reflux disease	no	no		nonerosive reflux disease

IBD = Inflammatory bowel disease; NR = not reported; n = number of studies analyzed; asterisk indicates availability of individual patient data.

Trials in Gastrointestinal Disorders

For gastrointestinal disorders, trials in IBS were meta-analyzed most frequently (n = 4), followed by inflammatory bowel diseases (Crohn's disease, ulcerative colitis; n = 3), FD (n = 2), and reflux disease and gastric and duodenal ulcers (n = 1 each). Two analyses in FD were based on individualized data [81, 82] (table 5).

One analysis only noted a higher PR in younger patients [77]; none reported gender differences in the PR.

Only a few disease and patient-related features predicted higher PR, especially inconsistent symptom pattern [81], symptom improvement during run-in [82], and a previous history of gastrointestinal symptoms [84].

Among the design features analyzed, a higher number of study visits was predictive of higher PR in ulcerative colitis [74], Crohn's disease [75], IBS [77, 79], while one report in IBS found high PR to be predicted by a lower

Table 6. Meta-analyses of RCT in other disorders

First author	Year	Ref.	n	Disease	Age	Sex	PR is higher with	PR is also higher with
Lee	2009	86	36	OAB	NR	NR		lower baseline severity
Thijs	1990	87	1*	hypertension	yes	NR	younger age	no other factor identified
Cho	2005	88	29	CFS	no	no		high intervention intensity
Freeman	1999	89	2*	PMS	yes	NA	younger age	no other factor identified
Lamel	2012	90	31	psoriasis	NR	NR		higher drug chance
Narkus	2013	91	6	allergy	NR	NR		no other factor identified
Kemeny	2007	92	1*	asthma	yes	no	younger age	no other factor identified
Wang	2012	93	34	asthma	no	no		lower baseline severity
McCall	2003	94	5	sleep disorders	NR	NR		no other factor identified
McCall	2011	95	1*	sleep disorders	yes	NR	younger age	no other factor identified

CFS = Chronic fatigue syndrome; PMS = premenstrual syndrome; NA = not applicable; NR = not reported; n = number of studies analyzed; asterisk indicates availability of individual patient data.

number of office visits [78]. Longer treatment follow-up [76] and higher frequency of drug application [83] were also predictive of the PR.

Trials in Other Diseases

Ten more meta-analyses report predictors from treatment trials for sleep problems (n = 2), asthma (n = 2), allergy (n = 1), psoriasis (n = 1), premenstrual syndrome (n = 1), chronic fatigue syndrome (n = 1), hypertension (n = 1) and OAB (n = 1), of which 4 were based on individual data (table 6).

Four analyses noted higher PR in younger patients [87, 89, 92, 95], while no study found an influence of gender on the PR.

A higher randomization ratio [90] was noted as a design factor driving higher PR in psoriasis, and lower symptom severity at baseline [86, 93] as patient-based factor driving the PR.

Discussion

This systematic review of systematic reviews, meta-analyses and meta-regressions demonstrates both disease-specific as well as disease-unspecific factors driving the PR in RCT, and these factors are either patient or design based.

Age and Gender

Taken together, our analysis indicates that age and gender appear not to play a role for PR in RCT: only 3 of 75 analyses could identify a contribution of sex towards the PR, and only 15 of the analyses found that PR are

higher in younger patients (mostly in psychiatric trials) while another 5 found the opposite. As we have seen especially in analyses involving children and adolescents with ADHD [52–54], these are based on a small number of studies included in the respective meta-analyses and therefore cannot outnumber the many more studies in adults that could not support this hypothesis. Even if the very young patients may show higher PR rates than adolescents and adults under specific circumstances [16], certainly among the three possible models (model 1: further decrease with higher age; model 2: stable after reaching adulthood; model 3: increase again in the elderly), model 2 is the most likely one: studies and analyses including the elderly (above 65 years) [65, 87] could not substantiate a further decrease of the PR in this group beyond that of adults.

It is of importance to note that our analysis grossly ignores quality differences in the type of statistical analysis substantiating the findings in the different meta-analyses, and that most studies were based on aggregate (study level) data. For proper patient-related predictors – such as age and gender – meta-analytic approaches based on individual patient data would be more appropriate, as was the case in 20 of the 75 analyses. But even if we only consider only these 20 reports, a similar picture emerges: 5 analyses noted younger age to be associated with higher PR, while 4 found older age to be the driving factor of the PR, and 11 did not find a contribution of age at all. Whether access to individual patient data for more RCT (e.g. in central repository) would allow another conclusion, needs to be shown in the future, but as long as access to individual drug trial data is predominantly controlled by the pharmaceutical industry, this will remain hope only [96].

A question remains that we cannot answer at this stage: why are sometimes average PR rates higher in children with ADHD, depression, and autism when compared to overall PR rates in the same condition in adults? The answer is presumably of methodological nature. In RCT, the response in the placebo arm of drug trials is usually a compound effect of different factors such as spontaneous variation of symptoms, regression to the mean, and the specific PR due to expectations and learning [4]. For the evaluation of the true drug benefit 'above placebo', separation of these factors is not necessary and is usually not performed. However, for the characterization of the 'true' PR, it would be essential to include a 'no treatment' control group to identify the contribution of the natural course of the disease [3] to both the drug- and the placebo-treated patients. If done so [97], nearly half of the effect seen in the placebo arm of RCT can be attributed to spontaneous variation of symptoms. With respect to the contribution of age of children, adolescents, adults, and elderly to the PR, a necessary consequence would be to test whether spontaneous variation of symptoms is similar in these different age groups within a single clinical condition (e.g. asthma), which is rather unlikely [98]. And even if so, the PR may still be higher in youth and women because of differences in pathophysiology.

While no-treatment controls are ethically questionable for serious medical conditions, an approximation of the size of spontaneous contribution to the PR in RCTs can be achieved using waiting-list controls that have their own methodological limitations [3] but are frequently conducted in nondrug trials, e.g. with psychotherapy [99]. In one meta-analysis [100] it was shown that the effect of waiting improved baseline depression scores by 33%, while placebo administration accounted for a 40% improvement. In another study, spontaneous improvement during waiting was 15% of Hamilton Depression Rating Scale (HAM) baseline values after 4–8 weeks waiting, and 20% of patients would respond to a degree that would be regarded as significant clinical improvement [101]. In the meta-analysis by Krogsbøll et al. [97], waiting contributed between 0 (insomnia) and 80% (depression) to the overall placebo effect across a variety of medical conditions.

Patient- and Disease-Based Factors

Among the patient-based predictors of the PR, the most prominent one that appears across all conditions and diseases except in gastrointestinal disorders is lower severity of the illness at baseline prior to randomization; this was noted in 18 analyses, and a few contrasting reports come only from neurological and psychiatric disor-

ders [28, 47, 53, 54, 66]. Usually, symptom severity is assessed via diagnostic criteria such as the HAM, the Unified Parkinson Disease Rating Scale, the Inattention/Overactivity with Aggression Conners parent and teacher rating scales in ADHD, and the Rome criteria in IBS, and cutoff criteria are used to ease and standardize enrolment. However, for most of the diseases listed here, these are predominantly physician or patient-reported outcome measures that are known to be susceptible to higher PR as compared to disease biomarkers [102, 103], and are also prone to manipulation during recruitment [104]. Furthermore, it has been shown that (in depression) physician and patient rating of disease severity may vary substantially [105]. The inclusion of patients with low symptom severity in RCT may also be in the interest of the drug industry [106] since it offers a larger market share once the drug has been approved.

Other patient-based or disease-based factors driving the PR have been noted occasionally in individual analyses, such as treatment naïvety in migraine [33], ADHD [52], and depression [69], symptom worsening before the start of the study in depression [62], but symptom improvement during run-in [82] and inconsistent symptom pattern [61] in FD, and early response to therapy [34]. It should be noted that in addition to the factors listed in the tables above, most studies noted more and other patient and design factors contributing to the PR.

Design-Based Factors

Three of the many factors identified in the meta-analyses stick out as prominent: more recently performed studies report higher PR rates than studies in the past [49, 50, 57, 60], more study visits during the trial [70, 73–75, 77, 79, 83], and studies randomizing more patients to drug than to placebo (called unbalanced randomization) [30, 37, 42, 68].

The first two are certainly correlated: over the last 25 years, trial designs have changed substantially from cross-over to parallel design, from 4 weeks to 8–12 weeks and even longer [3], and patient monitoring during the trial has intensified, e.g. by using electronic monitoring systems, resulting in more contacts of patients with doctors and trial staff. This underlines the importance of doctor-patient communication as underlying mechanisms for PR within and outside of clinical trials [3]. Associated PR-driving factors are longer trial duration [24] and longer follow-up observations [76]. It should be noted that the number of study visits was explicitly not a predictor of the PR response in pediatric trials in depression in children, while it was in adolescents and adults [70], indicating principle differenc-

es between children and adults. For children, the concept of ‘placebo by proxy’ has been put forward [107], but this needs to be explored further also for adults.

It appears also that in some indication areas (migraine, depression, IBS) European studies have produced higher PR rates than studies in the US [31, 32, 63, 80]. Whether this reflects systematic differences in design characteristics between Europe and the US remains to be shown, but it may be linked to more study sites and the increase in multicenter trials [41] in Europe.

The other factor, unbalanced randomization, is of different nature but has been noted as early as 1999 [30]. Recruiting more patients to drug than to placebo may be done for different reasons: for ethical reasons, to allow more patients to receive active treatment, for practical reasons to speed the recruitment process, or for pharmacological reasons, to test different drug doses or different drugs against a single placebo arm. This lowering of chances of patients to be randomized to placebo increases their expectations of subsequent symptom improvement and results in both higher drug as well as PR and decreases the drug-placebo difference, e.g. in depression [65]. This has also been confirmed in experimental studies, e.g. in Parkinson patients [108], and may be due to higher dopamine release as the underlying neurobiological reward mechanism [109].

We need to acknowledge limitations of our analysis. One is that we may have missed relevant information in

single RCT that may have – among others – analyzed determinants of the PR in addition to evaluating drug-placebo differences. We restricted ourselves to the analysis of papers (systematic reviews, meta-analyses, meta-regressions) that explicitly focused on the PR and quantified it because otherwise we would not have been able to cover all medical subspecialties simply due to the sheer number of RCT that have been published (more than 100,000). We also grossly ignored quality differences in the selected analyses and handled them all rather equally to extract predictor information, despite the fact that extraction errors in meta-analyses are known to be high [110]. This however, allowed us to attempt to screen the whole range of potential predictors of the PR – a quantification of these factors was never intended and may even be impossible. Finally, we focused on age and sex as moderators of the PR for this review and listed only one major patient- or design-based predictor per analysis for illustration reasons. Further analyses for single medical subspecialties will show whether or not our listing is unbalanced or incomplete, and likewise, whether age and gender have a different impact across different conditions.

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