ACCEPTABILITY OF DRUGS FOR MALE FERTILITY REGULATION: A PROSPECTUS AND SOME PRELIMINARY DATA

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ABSTRACT

Hormonal substances for male fertility regulation administered orally or by injection are currently undergoing clinical evaluation. These trials, sponsored by the World Health Organization, provide unique opportunities for intensive study of the acceptability of such an approach to fertility regulation, and of these drugs in particular. The research employs repeated interviews over a 15-month period and is conducted by social scientists collaborating with biomedical scientists at each of seven sites (Bangkok, Hong Kong, London, Mexico City, Santiago, Seoul, and Toronto). The focus is upon gauging male user's evaluations of hormonal methods (several androgen/gestagen combinations as well as cyproterone acetate) relative to their evaluations of other male methods they know about or have experienced. Of particular importance is to determine whether the hormonal methods modify or interefere with sexual desire, feelings, and behavior. The research is also assessing specific ways in which various perceived properties of fertility regulating methods relate to their acceptability in different socio-cultural settings.

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INTRODUCTION

Very few fertility regulating methods are available to men and among those available the two most effective ones, vasectomy and condoms, are considered unacceptable by many men. However, both withdrawal (coitus interruptus) and periodic abstinence are reported to be widely practiced (1, 2), suggesting the willingness of men in a variety of cultures to share responsibility for fertility control. It appears reasonable, therefore, to assume that the availability of a greater variety of effective and accceptable methods would probably increase the practice of family planning (3, 4).

Processes of developing and testing new fertility regulating methods (FRMs) have been described by Djerassi (5) who cites a variety of special problems associated with the development of male FRMs. Possible modes of regulating male fertility have recently been the subject of extensive review (cf., 6-11). Authors of each of these reviews as well as investigators reporting results of specific clinical trials (e.g., 12, 13) agree that new methods must not interfere with libido or potentia if they are to be acceptable to users, in addition to being non-toxic, effective and reversible.

Prominent among current efforts in FRM development is that of the Special Programme of Research, Development and Research Training in Human Reproduction within the World Health Organization (14, 15). In addition to pursuing research in numerous areas related to human reproduction, including the development of new FRMs for females, WHO is supporting basic and clinical research on the development of daily oral pills and monthly injectables for men (16). Some of the methods being studied, like the earlier-developed pill for women, contain hormones. During the time that these hormonal methods are undergoing clinical evaluation for toxicity, efficacy and other biomedically relevant criteria, questions of the methods' acceptability to the volunteers are simultaneously being pursued. A clearly important aspect of acceptability is whether the new methods will modify or interfere with male sexual feelings and performance, or have other unacceptable side effects. Therefore, given both general theoretical and clinical (17-19) evidence of possible effects of hormonal preparations on male sexual functioning, it is of particular importance to investigate this question in early clinical trials.

The importance of obtaining measures of sexual functioning is underlined by the following: (i) the widely-shared assumption (cf. 11), and the WHO survey finding (20) that any method believed to decrease male sexual performance or feeling would be unacceptable to men, (ii) the fact that the drugs being tested alter the pattern of secretion of testosterone, a result which might affect sexual interest as well as erectile or ejaculatory functions at some dosage levels (21-24), and (iii) the fact that a variety of drugs may have the potential to affect sexual behavior (25).

Studying the acceptability of a male FRM while it is undergoing clinical trial has an important advantage -- evaluations of the method (both its general acceptability as well as the salient perceived characteristics that determine its acceptability) are obtained from volunteers with first-hand experience with the method for a period ranging from 4 to 6 months. Despite the disadvantages of relatively small and unrepresentative samples, the approach of conducting acceptability studies among volunteers in a clinical trial clearly complements the field survey approach to studying the acceptability of male FRMs. For example, in a recently completed field survey (15, 20) in five countries -- Fiji, India, Iran, Korea, and Mexico -- relatively large representative samples of rural and urban men were asked to evaluate the acceptability of condoms and vasectomy as well as two hypothetical male FRMs (a daily pill and a monthly injectable). This field study, providing valuable data with which to compare the results of evaluations by volunteers in the current clinical trials, found that a high proportion of men expressed willingness to share responsibility for family planning. Moreover, a substantial majority of male respondents in most countries said they would use a male pill if it were available; a slightly smaller proportion said they would use a monthly injectable. In every setting but Mexico, where condoms were found to be least acceptable, men reported vasectomy to be far less acceptable than either condoms or any one of the two new methods. Other things equal, men apparently prefer a method with a relatively long duration of action and an oral rather than injectable route of administration. Irreversibility is considered highly undesirable whereas self-administration is seen as a positive attribute. Of considerable importance is the finding that in all countries surveyed, men uniformly agree in rating "decreased sexual pleasure" as a highly unacceptable feature of an FRM.

That the two contexts for studying acceptability of new FRMs, field survey and clinical trial, complement one another is evident in the fact that the weaknesses of each (small and possibly unrepresentative samples in the context of clinical trials, and evaluations of hypothetical rather than directly experienced methods in the survey study) are compensated for by corresponding strengths in the other approach.

Specific Objectives of the Acceptability Research in Clinical Trial

The research objectives may be summarized as follows: (i) To assess the acceptability of recently developed male methods both objectively, in terms of discontinuation rates, and subjectively, in terms of users' descriptions of characteristics of the method including experienced side effects, as well as in terms of users' general evaluative ratings of the method; (ii) As a corollary of the first objective, to examine whether accumulated experience with a method during the trial increases or decreases its general acceptability as determined by evaluative ratings; (iii) To compare users' evaluations of the new method with those of other male or female methods with which they have had experience; (iv) To assess the effects of the medication on various measures of sexuality

(self-reported desire for, frequency of, and enjoyment of sexual activity, as well as incidence of problems in sexual performance); (v) To determine whether dose level of the medication influences acceptability, sexual feelings and performance, or reports of any other side effects.

A considerably more general implicit objective is to develop, test, and refine specific instruments and generalizable methodological strategies to facilitate collaboration between biomedical and social scientists in future large scale clinical trials.

METHODS AND MATERIALS

General Format of Clinical Trial

After initial examination and admission to the clinical trial, volunteers continue to be examined by a physician or nurse every two weeks during a 12-week Pre-treatment phase. This Pre-treatment period, necessary to establish baselines for physiological and behavioral measures, is followed by a 24-week Treatment phase (except in Hong Kong where the Treatment phase lasts 16 weeks), and finally a 24-week Post-treatment or Recovery phase.

The specific medications and dosage levels being tested are shown in Table I; three of the research settings include an inert zero dosage level substance in a placebo control group. Table I also presents the number of volunteers scheduled at each dosage level, the duration of treatment, specific pharmaceutical agents as well as route of administration.

Volunteers are given a description of possible side effects of the drugs including weight gain, acne, gynacomastia, and decreased libido and are told that one purpose of the trial is to identify whether these and other side effects occur. After informed consent is obtained, volunteers are assigned (randomly, where permitted) to the dose groups and, except in Toronto, are not informed of their dose level to minimize effects attributable to volunteers' expectations. Volunteers are instructed to have their partners continue reliance on an effective female-targeted contraceptive method, e.g. pill or IUD, for the duration of the trial since the project is a dose-finding exercise and therefore some dosage levels of the drugs tested may not induce oligospermia to a level which may be considered in the infertile range. Volunteers receive incentive payments for their time and effort in appearing at the clinic biweekly to provide semen and blood samples and to undergo the required medical examination.

Table I: Pharmaceutical Preparations, Dosage Levels, and Other Parameters of the Clinical Trials

Research Center	Pharmaceutical Preparations and Dosage Level		Number of Volunteers Scheduled At Each Dose Level (& Total)	Duration of Treatment in Weeks
	Androgen	Gestagen		
Bangkok	Testosterone oenanthate	Medroxyprogesterone acetate		
	(mg monthly injection)	(mg orally daily)		
	250	5	5	24
	250	10	5	
	250	20	5	
	500	20	5	
			(20)	
London	Testosterone oenanthate	Medroxyprogesterone acetate		
	(mg monthly injection)	(mg orally daily)		
	200	5	8	24
	200	10	8	
	200	20	8	
	0	0	8	
			(32)	
Mexico City	Testosterone oenanthate	17α-hydroxyprogesterone caproate		
	(mg monthly injection)	(mg injections)		
	250	0	10	24
	250	250 monthly	10	
	250	250 bimonthly	10	
			(30)	
Santiago	Testosterone oenanthate	Depot-medroxyprogesterone acetate (mg monthly injection)		
	(mg monthly injection)			
	0	0	8	24
	200	100	8	
	200	200	8	
			(24)	
Seoul	Testosterone cypionate	Depot-medroxyprogesterone acetate (mg monthly injection)		
	(mg monthly injection)			
	200	200	10	24
	200	400	10	
	400	200	10	
			(30)	
Toronto	Methyl testosterone	Medroxyprogesterone acetate		
	(mg orally daily)	(mg orally daily)		
	10	5	6	24
	10	10	6	
	10	20	6	
	20	20	6	
			(24)	
Hong Kong	Cyproterone acetate			
	(mg orally daily) 0		10	16
	5		10	
	10		10	
			(30)	

Criteria for Selection of Volunteers

Admission to the trial is based on demographic, behavioral, and biomedical criteria; volunteers should be in the age range of 25 to 45 and in good health, have sperm counts in excess of 20 million per cc, be free of a history of active or chronic disease, and exhibit willingness to participate in both the biomedical and acceptability components of the research.

Study Settings

The seven sites in the project (Bangkok, Hong Kong, London, Santiago, Mexico City, Seoul, and Toronto) were selected for the acceptability research because they were sites for WHO-supported clinical trials and a social science collaborator was available. An additional objective was to include in the study some sites that participated in the earlier large-sample survey of hypothetical male methods, and to obtain data from clinical settings in different parts of the world.

Research Instruments: Development and Administration

Four interview schedules, pre-tested in several settings, are administered by a local interviewer fluent in the language of the volunteers. Skilled interviewers establish good rapport, reassure volunteers about confidentiality, and thus maximize truthful responding. The interview schedules themselves were translated at each center from English into the local language, with independent back-translation into English to aid in achieving conceptual equivalence among forms at all centers.

Interview questions employ a variety of formats; some use a two-stage Likert scale, some a modified Cantril ladder rating scale, and still others employ magnitude estimation techniques for dimensions having a familiar natural scale such as frequency. Items were constructed to enable assessment of both temporal stability (test-retest reliability) as well as internal consistency of responses.

Pre-treatment Acceptability Interview --. This interview, given at the beginning of the Pre-treatment phase, obtains demographic and socio-economic information about the volunteer, his marital status, number of children, contraceptive history, expectations about the new method, evaluations of the new method and of others, as well as reasons for participating in the clinical trial. The interview also assesses the importance of various perceived attributes (26) that may determine both the overall acceptability of a method as well as intentions to use it in the future.

Sexuality Interview --. Also administered at the beginning of the volunteer's participation in the clinical trial and thereafter every four weeks (every second visit to the clinic), this interview assesses the volunteer's sexual behavior and feelings in terms of reported frequency of various sexual activities and in terms of the volunteer's perception of changes over time in sexual desire and

frequency of erectile or ejaculatory problems. Effects of different dose levels of the drugs on self-reported sexual functioning is assessed by comparing measures over time among groups exposed to different dosage levels.

Follow-up Acceptability Interview --. Patterned after the Pre-treatment Acceptability Interview, this interview inquires in detail about the volunteer's evaluation of the specific new method he is experiencing compared to available alternatives, his perception of selected attributes of the new method, and his satisfaction with aspects of the clinical trial not directly related to the method per se. It is administered to the volunteer midway through the Treatment phase and again, midway through the Post-treatment phase to determine whether experience with the method changes the volunteer's perception and evaluation of it.

Discontinuation Interview --. Only those volunteers who decide to discontinue participation in the clinical trial before they have completed all phases are given this interview. Administered whenever the volunteer permits, this interview focuses on reasons for discontinution, whether medical, psychosocial, method-related, or delivery system-related.

PRELIMINARY RESULTS

General Progress, Prospects for Completion, and Number of Continuing Volunteers --. Data collection at Bangkok, Hong Kong, Seoul, and Toronto has been completed and Santiago is scheduled for completion by mid-1979*. Two centers, Seoul and Toronto, had biomedical clinical trials already underway when the acceptability research began, thus obviating the possibility of obtaining data from all volunteers at these two centers. None of the centers except Mexico City have experienced excessive difficulty recruiting sufficient volunteers. In some settings, especially in Hong Kong and Santiago, there has been a discontinuation problem during the Pre-treatment phase (i.e., prior to the administration of any of the scheduled medication) but even in these settings, volunteers who begin Treatment are highly likely to continue in the study. In Hong Kong where the incentive payment was very low, it was necessary to recruit initially approximately three times the number of volunteers planned in order to retain the scheduled number of continuing participants, and in Santiago it was necessary to recruit approximately twice the number planned. Analyses of the responses of discontinuers will determine whether features inherent in the clinical trial, e.g. providing bimonthly blood and semen samples, or extraneous conditions

*As of November 1978, it became doubtful that the biomedical scientists in London and Mexico City would be able to complete the clinical trial as scheduled; discontinuation of the clinical trial at these sites was not caused by either general community displeasure with the study, or the unwillingness of recruited volunteers to continue.

were the chief deterrents to continued participation. In any case, adverse reactions to the medication does not appear to be a cause of discontinuation of the trial.

Clearly, one of the most important and reassuring results obtained to date is the demonstration that in a variety of socio-cultural settings, it is possible to conduct an intensive and systematic study over time of men's sexual attitudes, behavior, and feelings in response to a hormonal FRM. The fact that data collection has nearly been completed provides reassurance that the worst initial fears among members of the Task Force were unfounded -- fears that an acceptability study focusing on sexual functioning risked the alarm and censure of members of the communities in which the studies were done, as well as fears that the study might be infeasible because individual volunteers would resist inquiry into a domain as sensitive, private, and taboo-laden as their sexual behavior and feelings. The discovery that it is possible to conduct such studies in various parts of the world is of considerable importance, especially in view of the wide-spread recognition of the intimate relationship between contraceptive and sexual behavior.

Several highlights from preliminary analyses are presented here; a report of the completed study will be forthcoming as soon as the study is completed. The current summary of results of the Pre-treatment Acceptability Interview (P-TAI) and the first two administrations of the Sexuality Interview (SI) is based on analysis of data from 202 volunteers distributed according to center as follows: Bangkok, 25; Hong Kong, 51; London, 36; Mexico City, 10; Santiago, 57; Seoul, 10; and Toronto, 13. The number of respondents completing the first two administrations of the SI are the same in Bangkok, Mexico City, and Seoul, but fewer in other settings. The number of volunteers who are expected to complete all phases of the trial is 102 distributed as follows; Bangkok, 25; Hong Kong, 28; Santiago, 26; Seoul, 10; and Toronto, 13. This estimate excludes the doubtful 24 and 10 cases from London and Mexico City, respectively.

Family Planning Experience and Intentions of the Volunteers --. With only slight variation across centers, most volunteers already have one or two children (only 13% have more than three children), 60% plan to have no more and 58% believe their partner plans no more children. On the average, the volunteers have had some experience, either directly or via their partners, with three different methods of fertility regulation; the pill for women (71%), IUD (40%), rhythm (24%), foam (18%), and abortion (14%) are most frequently described as "ever used" by their partners. The men themselves report having "ever used" condom (60%), withdrawal (35%), and abstinence (17%), in that order. Back-up methods being relied upon during the clinical trial are the female pill (30%), IUD (19%), and condom (15%). Somewhat disturbing is the report by 17% of the volunteers that they are using no back-up method in spite of the protocol advising all volunteers to ensure continuing use of an effective back-up method.

In general, the volunteers or their partners have had experience with a variety of FRMs and show considerable interest in using effective contraception in the future. In explaining their reasons for volunteering for the clinical trial, "helping science", "men should do their share", "need for money", and "to learn something for myself" were most frequently cited.

Acceptability of Both New and Familiar Methods --. Several different methods of assessing acceptability (rank ordering, summing positive attributes, rating intention to use, etc.) agree that the new method, whether in the form of a daily pill or a monthly injectable, has the highest acceptability, followed by vasectomy and condom. Volunteers also strongly agree in preferring methods that are self-administered rather than given by a health provider, and in being unfavorable toward a method that is irreversible. Each of these generalizations is based on answers to one or more specific items in the Pre-treatment Acceptability Interview; specific details on item wording and responses will be presented in the forthcoming final report.

Volunteers initially give the benefit of the doubt to the new method they are trying, i.e., they almost uniformly disbelieve statements attributing possible negative features to the new method (e.g., decreased ejaculate, embarrassing to obtain, interferes with man's pleasure or desire, interferes with woman's pleasure or desire, bad for health, bad psychologically, leads to promiscuity, takes too long to become infertile). One exception to this generalization is that in Bangkok men exhibit some concern that it may "take too long" to regain fertility once they cease taking the medication. Whether the general favorable reactions to the new method are strengthened or weakened as a result of direct experience with the new method is a matter of chief interest that will be known once the study is completed.

Being "liked by women" appears to be one attribute that volunteers in all settings single out as highly characteristic of the new methods whether pill or injectable. Furthermore, a man's stated intention to use a given method, whether the new FRM, or condom or vasectomy, in the future is closely related to his belief that the method in question is liked by women.

Irreversibility appears to be the most negative feature of vasectomy in the view of the volunteers; as a corollary it apears that a reversible form of vasectomy would maximize those attributes that promote its acceptability. The effectiveness and relative inexpensiveness of vasectomy appear to be its two most positive attributes, although the fact that it is seen as "liked by women" is also a strong positive factor.

Coitus-dependence and consequently frequency of use appear to be distinct disadvantages of condoms, in addition to the fact that men almost uniformly agree that "condoms decrease a man's sexual pleasure".

When confronted with a list of six types of methods, both real and hypothetical and all described as "equally effective and having no

undesirable side effects", volunteers displayed the following preference order (from most to least preferred): 3-monthly injectable, monthly injectable, weekly pill, daily pill, coitus-dependent method, permanent method. Average ranks tended to be quite similar in all settings, and also impressively similar to those obtained in the recently completed five-country field survey study sponsored by WHO (15, 20).

Average ranks of these six types of methods appear quite stable over time when rankings obtained at the beginning of Pre-treatment are compared with those obtained on a subset of 104 volunteers six months later during Treatment. Moreover, across the same six-month interval, volunteer's ratings of their intention to use the new method after the clinical trial is completed display a rather high stability coefficient (Pearson r of .72).

In general, when asked why they prefer a particular method, volunteers agree that effectiveness, ease of use, and lack of physical or psychological side effects are important considerations; volunteers are likely to ascribe any dislike of a method to the fact that it interferes with sexual pleasure, has physical side effects, is permanent, is not effective, and is not approved by tradition, religion, or peers.

Measurement of Sexual Functioning --. Monthly administration of the Sexuality Interview during the clinical trial provides a rich and a voluminous array of information on self-reported sexual functioning over time and in response to different dose levels of medication in each of the research settings. Whether the drugs tested adversely affect male sexual performance and desire can be answered only if there are reliable, internally consistent, and theoretically meaningful measures of important dimensions of male sexuality. In the absence of generally accepted measures of male libido, sexual drive, or motivation, initial efforts have been directed toward constructing a set of clear and reliable scales to measure this domain. Beach (21), who is a widely-recognized authority in this area, has argued that our understanding of theoretical terms such as "libido" must eventually be derived from statements about the frequency and intensity of specific kinds of sexual behavior. He suggests the desirability of measuring such objective variables as the speed and magnitude of penile erection, the duration and intensity of physical stimulation necessary for orgasm, the number and strength of muscular contractions in sexual climax, the duration of the post-orgasmic refractory period, as well as the frequency of intercourse and masturbation (21, pp. 264-265). Because the Sexuality Interview relies upon self-report, it assesses only the latter two of Beach's recommended list of objective measures. However, volunteers also report on their frequency of thoughts and feelings about sex, their frequency of morning erections, as well as a variety of subjective measures concerning degree of interest in, pleasure from, and satisfaction with their sexual functioning. In addition, volunteers report the incidence of erectile and ejaculation problems, whether their experience during the last four weeks has been typical, and the incidence of a variety of environmental-interpersonal

conditions that may enhance or limit opportunity for sexual activity. In all, a set of approximately 80 separate questions about sexual attitudes, feelings, and behaviors, administered sixteen times over the course of the clinical trial, provides a large challenge for data reduction. Considerable effort, therefore, has been placed initially on the methodological issues of instrument development and testing. The results to date may be succinctly summarized as follows:

1. Individual items display remarkably good temporal stability (test-retest reliability) from one month to the next during the entire Pre-treatment phase, with stability coefficients (Pearson r) averaging greater than .40. Given that single items are reasonably reliable, it is clear from general test theory that composite scores based on groups of intercorrelated individual items are likely to yield even higher test-retest reliabilities. The latter assumption will soon be tested.

2. There appear to be small but reliable differences among centers in the frequency and intensity of sexual activities during Pre-treatment. For example, rated enjoyment of sexual thoughts and feelings, as well as frequency of sexual thoughts and feelings, of morning erections, and of sexual intercourse are examples of variables for which there are center differences. These center differences in baseline (Pre-treatment) values must of course be taken into account in the analysis of the effects of medication on various sexuality measures. Variables displaying insignificant center differences include frequency of self-reported premature ejaculation, intensity of sexual desire, recent changes in frequency of intercourse, and recent changes in the quality of sexual activity.

3. In spite of the above-noted cultural differences in some reported sexual behaviors, factor analytic procedures yield a stable set of at least three independent dimensions or principal components among the variety of questions. The general factor structure that emerges remains invariant in spite of variations in type of data (whether raw score or center-standardized scores for removal of center differences), in whether the analysis is performed separately in large centers or on data pooled from all centers, and in whether the analysis is done with the first or second administration of the Sexuality Interview.

   The summarized "factors" are clinically and theoretially sensible. For example, one cluster of variables consists of self-rating scales describing the degree of interest, enjoyment, pleasure, and satisfaction associated with sexual behavior as well as frequency of sexual intercourse and satisfaction with the relationship with one's partner. Another is a set of variables describing recent changes; a third cluster appears to measure the problem of premature ejaculation and consequent partner dissatisfaction; frequency of masturbation and frequency of morning erections are examples of items that appear independent of each of the above mentioned clusters.

4. The use of a small subset of "factors" or "clusters of variables" may enable more succinct representation of the sexuality domain than does the original set of 80 variables, thus permitting a clearer focus in the next step of the analysis in which two major questions will be addressed:

   (a) Does the medication given in Treatment have dose-related effects on any of the measures of sexual functioning?

   (b) Do medication-induced changes in sexual functioning, if any are found, adversely affect the acceptability of the method being tested in the clinical trial?

SIGNIFICANCE OF THE RESEARCH

The seven-country study of acceptability and effects on sexuality of new male contraceptive drugs, administered via daily pill or montly injection, provides an occasion to investigate a variety of important questions. The study is assessing the way in which a variety of directly experienced and expected attributes of a method determine its acceptability. Further, the study will assess the relation between acceptability and biomedical parameters of the clinical trial such as pharmaceutical preparation and dose level; in particular the study will examine whether the drugs tested interfere with sexual functioning or have other side effects that impinge adversely on acceptability.

The fact that this cross-cultural research is organized under the aegis of a multinational organization (WHO) provides the advantage of a common protocol in a variety of conditions and thus the likelihood of generating data for which cross-cultural comparisons are meaningful. The project may also yield better understanding of the subtle mix of conditions that maximize cross-cultural and cross-disciplinary cooperation in efforts to solve a problem of great importance and magnitude -- the development of safer, more effective fertility regulating methods that are acceptable in a variety of different socio-cultural settings.

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