CHAPTER 7

Time-Dependent Psychotropic Drug Effects:
Hints of Pharmacochronomics, Broader than Circadian Time Structures

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Abstract

The importance of timing medications is noted in the context of the effects of psychotropic drugs. The information here assembled as yet is examined mostly by inspection with the unaided eye and conventional (rather than time series-related) statistics. An effect of time, shown by an analysis of variance, however, awaits an inferential statistical estimation of the cycles' parameters and of their uncertainties. In summarizing drug effects, only peak times may be tabulated—time-macroscopically (tm) as clock-hours and times in relation to the synchronizing 12-hourly alternation of light and darkness, a proxy for a marker rhythm. A large body of such carefully collected information here included, however, awaits further time-microscopic (tmi) computer-implemented time series analyses that rely on all available data. Among many other procedures, curve-fitting assesses the uncertainties involved in detecting a reproducible rhythm and/or provides interval as well as point estimates of parameters, such as amplitudes, A, and acrophases, \( \phi \), when a single component is fitted. The magnitude and orthophase are the predictable extent of change within a cycle and peak of the fitted model when two or more components are considered. The period involved should be estimated as soon as the length of the time series permits. The A and \( \phi \) values here computed from mean values taken off a graph should be only an incentive to tmi analyze the original data, so that charts can be mapped that are based on all of the data, rather than depending on the vagaries of peak locations.

Putative mechanisms underlying variations, if not rhythms, in drug efficacy are noted. Some tmi considerations are added as concepts and tools for further work that takes more than synchronization with the lighting regimen and/or an obvious living routine into account. Chronomes—time structures, consisting of deterministic and other chaos, trends and a broader-than-circadian spectral element—are pertinent to pharmacology. Chronomes in us resonate with chronomes in our environment, far beyond the photic day and calendar year. Whether the transyears, e.g., of \(-1.3\) and/or \(1.6\) years, among other biological (evolutionary?) near-matches of non-photic environmental cycles are also pertinent to the time-structure-based pharmacochronomics of psychotropic drugs prompts the suggestion to collect data replicated along the scales of months and years as well as along that of a day. Estimations of the characteristics of circadian, circaseptan or circannual rhythms based on just one cycle in a day, a week or a year are comparable to taking the pulse for only a heartbeat, i.e., one second! Treatment timed by marker rhythm, rather than by clock-hour, can not only save the amount of needed drug and reduce side effects; it also aims at optimizing the conventional desired effect and to pursue the goal of detecting new effects by focusing on elevated disease risk and the timely development of countermeasures. In the field of drugs affecting sleep and broader brain function, the importance of assessing time structure remains a worthwhile challenge, based on evidence that constitutes a complementary system to the partial system of timing psychotropic drugs.

A Broad Rhythm Spectrum

Most physiologic functions have a rhythm with one cycle in approximately 24 hours, among many other rhythms with frequencies covering over 10 orders of magnitude. There are also trends with age or disease risk elevation and changes resolvable as probabilistic or other chaos. The endpoints of rhythms, trends and chaos constitute chronomes (time structures). Mechanisms underlying chronomes are the topic of chronobiology, the study of diversity in time, complementing genetics, the study of diversity in space. Genetics led after 1950 to chronobiology, and eventually to genomics, the mapping of genomes. Chronobiology led to chronomics, the mapping of chronomes in us that resonate with, or are synchronized by, chronomes around us. Chronomics are concerned with mapping the characteristics and uncertainties of changes with time of variables in us and in our environment near and far. Like many other phenomena, drug efficacy varies markedly as a function of chronomes, among others along the scales of 24 hours (e.g., refs. 19-31) and the seasons.

To be investigated are the roles played by rhythms of non-photic origin, such as the week, about half-weekly, about 8-hourly, about-half-yearly, about 1.3 to about 1.6-yearly (transyearly), periods, as well as circadecadals, circadecadals and circquindecadals, that may contribute to unwarranted "substitution" therapy, implemented in ignorance of circadecadal cycles. Infraadian rhythms in still broader chronomes remain a challenge to endeavors in diagnosis or treatment, including the use of psychotropic drugs, such as...
antipsychotics, antidepressants, mood stabilizers, benzodiazepines, barbiturates, psychostimulants, and a variety of neurotransmitter agonists, in view of infradian cycles documented by Derer, Gjessing, Reimann and Richter, among others. The variations in drug effects may not be due exclusively and probably not primarily to the stage of rhythms documented for the pharmacokinetics of many drugs, but may stem substantially from a partly built-in, lighting- and temperature-regimen-independent rhythm in susceptibility-resistance, documented for ethanol effects in alternating light and darkness and shown by 1960, Figure 1, to persist in the absence of this lighting regimen. The task of aligning this effect upon the brain and many others with circadian rhythms in the intracerebral neurotransmission system, shown in the tma Figures 2A and B and the tmi Figures 2C-E is a halting first step toward focus upon mechanisms.

**Puzzles**

Among biologists in 1949, fixing the time of day was deemed a sufficient precaution to "eliminate the effect of rhythms" and (for far too many, as now) repeated sampling at different clock-hours was regarded as sufficient for an approach to assess the effect of drugs on what became circadian rhythms. In 1949, counts of certain circulating blood cells using (as controls) a 24-hour synchronized group of mice were compared with counts from another group on the same lighting regimen; results from comparisons of the same two groups at different clock-hours led to different, even opposite results, since one of the groups was phase-shifted by a diet restricted in calories offered in the morning, usually a time of rest for nocturnally feeding mice, as realized before publication (details in refs. 1 and 55). The same results cannot be expected when comparing the same two phase-shifted groups at different times of day.

**Figure 1.** The statistical significance of an anticipated (!) circadian rhythm can be validated by the rejection of the zero-amplitude (no circadian rhythm) assumption with the cosinor method. The procedure of standardization of the experimental animal laboratory by rendering the lighting regimen as constant as possible (e.g., by instituting continuous darkness, as in the case of the study presented herein, or by continuous light, and by providing a controlled temperature, reducing noise and other obvious stimuli, notably cyclic ones) has been used for half a century to demonstrate an independence from the lighting regimen, no more. The endogenicity of circadians is supported in many cases by the results of molecular biology. Results in continuous darkness, however, do not suffice to prove it, although they support this hypothesis. © Halberg.

**Figure 2A.** Tma time course along the 24-hour scale of murine hypothalamic 5-hydroxytryptamine (5-HT); expressed as % of series mean. Tmi quantification required to estimate any age-dependent amplitudes shown elsewhere. Original data of Bhaskaran and Radha. © Halberg.

**Figure 2B.** Tma approach reveals age-dependent differences in the circadian timing of dopamine and norepinephrine but not of 5-hydroxytryptamine (5-HT) in data pooled from 6 brain areas; original data from each area expressed as % of series mean and pooled to construct the curves here shown, analyzed elsewhere and in Figures 2C-E. Original data of Bhaskaran and Radha. © Halberg.