- Bayesian theory was originally developed to improve forecast accuracy by combining subjective prediction with improvement from newly collected data.

- In the diagnosis of disease, the physician may make a preliminary diagnosis based on symptoms and physical examination. Later, the results of laboratory tests are received. The clinician then makes a new diagnostic forecast (پیش بینی کردن) based on both sets of information.

- Bayesian theory provides a method to weigh the prior information (eg, physical diagnosis) and new information (eg, results from laboratory tests) to estimate a new probability for predicting the disease.

- In developing a drug dosage regimen, we assess the patient's medical history and then use average or population pharmacokinetic

parameters appropriate for the patient's condition to calculate the initial dose. After the initial dose, plasma or serum drug concentrations are obtained from the patient that provide new information to assess the adequacy of the dosage.

The dosing approach of combining old information with new involves a "feedback" process and is, to some degree, inherent in many dosing methods involving some parameter readjustment when new serum drug concentrations become known.

The advantage of the Bayesian approach is the improvement in estimating the patient's pharmacokinetic parameters based on Bayesian probability versus an ordinary least-squares based program.

- From knowledge of mean population pharmacokinetic parameters and their variability, Bayesian methods often employ a special weighted least-squares (WLS) approach and allow improved estimation of patient pharmacokinetic parameters when there is a lot of variation in data.

Example:

After diagnosing a patient, the physician gave the patient a probability of 0.4 of having a disease. The physician then ordered a clinical laboratory test. A positive laboratory test value had a probability of 0.8 of positively identifying the disease in patients with the disease (true positive) and a probability of 0.1 of positive identification of the disease in subjects without the disease

(false positive). From the prior information (physician's diagnosis) and current patient-specific data (laboratory test), what is the posterior probability of the patient having the disease using the Bayesian method?

Solution:

Prior probability of having the disease (positive) = 0.4

Prior probability of not having the disease (negative) =

1 - 0.4 = 0.6

Ratio of disease positive/disease negative = 0.4/0.6

= 2/3, or, the physician's evaluation shows a 2/3 chance for the presence of the disease.

. The probability of the patient actually having the disease can be better evaluated by including the laboratory findings. For the same

patient, the probability of a positive laboratory test of 0.8 for the detection of disease in positive patients (with disease) and the probability of 0.1 in negative patients (without disease) are equal to a ratio of 0.8/0.1 or 8/1.

. This ratio is known as the likelihood ratio. Combining with the prior probability of 2/3, the posterior probability ratio is:

Posterior probability ratio = (2/3)(8/1) = 16/3

Posterior probability = 16/(16+3) = 84.2%.

. Thus, the laboratory test that estimates the likelihood ratio and the preliminary diagnostic evaluation are both used in determining the posterior probability.

. The results of this calculation show that with a positive diagnosis by the physician and a positive value for the laboratory test, the

probability that the patient actually has the disease is 84.2%.

·Bayesian probability theory when applied to dosing of a drug involves a given pharmacokinetic parameter (P) and plasma or serum drug concentration (C), as shown below. The probability of a patient with a given pharmacokinetic parameter P, taking into account the measured concentration, is Prob (P/C):

$$\text{Prob}(P/C) = \frac{\text{Prob}(P) \cdot \text{Prob}(C/P)}{\text{Prob}(C)}$$

where

Prob P = the probability of the patient's parameter within the assumed population distribution

Prob(C/P) = the probability of measured concentration within the population

Prob (c) = the unconditional probability of the observed concentration

-Example:

- Theophylline has a therapeutic window of 10-20 µg/mL.
- Serum theophylline concentrations above 20µg/mL produce mild side effects, such as nausea and insomnia; more serious side effects, such as sinus tachycardia, may occur at drug concentrations above 40µg/mL; at serum concentrations above 45µg/mL, cardiac arrhythmia and seizure may occur. However, the probability of some side effect occuring is by no means certain.
- Side effects are not determined solely by plasma concentration, as other known or unknown variables (called covariates) may affect the

side-effect outcome. Some patients have initial side effects of nausea and restlessness (even at very low drug concentrations) that later disappear when therapy is continued.

The clinician should therefore assess the probability of side effects in the patient, order a blood sample for serum theophylline determination, and then estimate a combined (or posterior) probability for side effects in the patient.

- The decision process is illustrated graphically in the following figure:

The probability of initial (prior) estimation of side effects is plotted on the x axis, and the final (posterior) probability of side effects is plotted on the y axis for various serum theophylline concentrations.

- For example, a patient was placed on

theophylline and the physician estimated the chance of side effects to be 40%, but therapeutic drug monitoring showed a theophylline level of 27 μg/mL. A vertical line of prior probability at 0.4 intersects curve a at about 0.78 or 78%.

Hence, the Bayesian probability of having side effects is 78% taking both the laboratory and physician assessments into consideration.

The curves (a-e in following Fig) for various theophylline concentrations are called conditional probability curves.

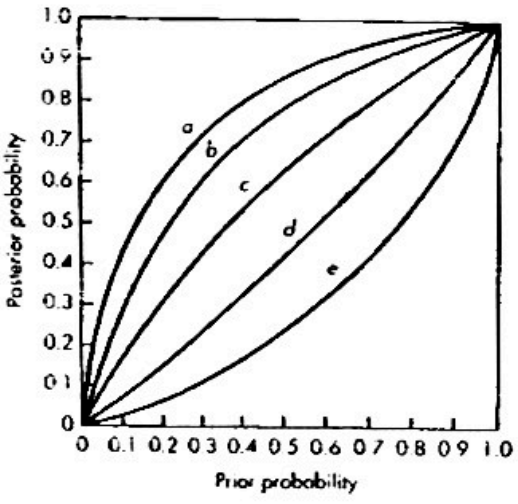

Figure Conditional probability curves relating prior probability of toxicity to posterior probability of toxicity of STC. theophylline serum concentrations [a] 27–28.9; [b] 23–24.9; [c] 19–20.9; [d] 15–16.9; and [e] 11–12.9 (all STC in μg/mL).
(From Schumacher, 1995, with permission.)

□ Applications:

. Bayesian theory does not replace clinical judgment, but it provides a quantitative tool for incorporating subjective judgement (humans) with objective (laboratory assays) in making risk decision. When complex decision involving several variables are involved, this objective tool can be very useful.

- Bayesian probability is used to improve forecasting in medicine.
- Bayesian parameter estimations were most frequently used for drugs with a narrow therapeutic ranges such as aminoglycosides, digoxin.
- The technique has now been extended to cytotoxic drugs and warfarin.
- Bayesian method have also been used to

limit the number of samples required in more conventional pharmacokinetic studies with new drugs.

• Disadvantage:

-is the subjective selection of prior probability. Therefore, it is not considered to be unbiased by many statisticians for drug approval purposes.